EPA-560/11-80-015
June 1980

SUPPORT DOCUMENT
HEALTH EFFECTS TEST RULE:
CHLOROMETHANE

ASSESSMENT DIVISION
OFFICE OF TOXIC SUBSTANCES
Washington, D.C. 20460

U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES AND TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

CONTENTS

INTRODUCTION

In its first report to the EPA in October 1977, the Toxic Substances Control Act Interagency Testing Committee (TSCA ITC) recommended that chloromethane be given priority consideration for the development of testing requirements under Section 4 of the Toxic Substances Control Act (TSCA ITC 1978). Specifically, the ITC recommended that chloromethane be tested for its carcinogenicity, mutagenicity, teratogenicity, and other chronic effects. With regard to chronic effects, the ITC expressed particular concern for chloromethane's effects on the central nervous system, liver, kidney, bone marrow, and the cardiovascular system.

On the basis of information presented in the following sections, the EPA is proposing that chloromethane be tested for oncogenicity and structural teratogenicity. This document supports the EPA's proposed test rules requiring such testing. Test standards for oncogenicity and structural teratogenicity have been proposed.

In addition the EPA is recommending that chloromethane be tested for potential chronic neurotoxic effects, mutagenicity, and behavioral teratogenicity but is not proposing testing at this time. Because the EPA has not yet proposed test standards for chronic neurotoxic effects, behavioral teratogenicity, or some of the mutagenicity tests, the Agency is deferring proposal of test rules. The EPA is requesting comment from the public on the pertinent issues set forth in this document and the accompanying Preamble pertaining to such testing.

The EPA has concluded that sufficient information is already available to evaluate chloromethane's effects on the liver, kidney, bone marrow, and cardiovascular system. Thus, testing will not be required.

I. Identity of Chloromethane

Chloromethane, CH_3Cl, (also known as methyl chloride) is a colorless, noncorrosive gas at room temperature and normal atmospheric pressure. Other physical properties of this chemical include: molecular weight, 50.49; boiling point, -23.7°C; melting point, -97.6°C; specific gravity, 0.92 at 20°C; solubility in water, 0.74 g/100 ml at 25°C (DeForest 1979); vapor pressure, 5 atm at 20°C; and an estimated logarithm of the octanol/water partition coefficient (log P_{oct}) of 0.91 (Hansch et al. 1975).[1]

Almost all of the chloromethane produced in this country (greater than 98 percent) is made by the hydrochlorination of methanol (Lowenheim and Moran 1975, CMR 1976). Ahlstrom and Steele (1979) state that two grades of chloromethane are produced, the technical and the refrigerant. The refrigerant grade must be very pure to prevent attack on the refrigeration equipment by impurities present in the chloromethane, and generally contains less than 75 ppm water. These authors give the known contaminants of a technical grade product as no more than 100 ppm H_2O, vinyl chloride, ethyl chloride and residue, 50 ppm methanol and acetone, 20 ppm dimethyl ether and 10 ppm hydrogen chloride. It has also been reported that chloroform (trichloromethane)and carbon tetrachloride (tetrachloromethane) are obtained as coproducts in the production of chloromethane by the hydrochlorination of methanol (SRI Undated, SRI 1979a), so that possible contamination by these products may also occur. Table 1 compiles information obtained through personal communication with several companies on purity and contaminants of their products.

[1]With the exception of the solubility in water and the log of the octanol/water partition coefficient, all physical properties were obtained from recent editions of the CRC Handbook of Chemistry and Physics (1978) and the Merck Index (1976).

Table 1. Chloromethane Purity and Some Contaminants

Specifications	Allied	Ansul	Conoco	Diamond Shamrock	Dow Chemical [a]	Dow Corning	Ethyl [b]	GE	Stauffer	Union Carbide
Minimum Purity (%)	99.8	99.5	99.95	99	99+	99.5	99.5		99.8	99.5
Maximums: Water (Moisture)(ppm)	80	80	80		100	80	100	150	60	80
Acidity (HCl)(ppm)	5	10	10		10	10	10	100	40	3,000
Nonvolatile Residue (ppm)	5	100	100		100		100	100	30	
Dimethyl Ether (ppm)		20	50		20	20	20		15	100
Acetone (ppm)					50	50	50		1-2	50
Methanol (ppm)					50	50	50		1-2	50
Ethyl Chloride (ppm)									100	100

a Dow 1978.
b Ethyl (n.d.).

The direct chlorination of methane produces a small amount of chloromethane (less than 2 percent), in which case there is the potential for contamination with dichloromethane, chloroform, and carbon tetrachloride, in order of importance (Lowenheim and Moran 1975).

II. Exposure Aspects

A. General

The TSCA Inventory (OPTS 1980) states that the production range (includes importation volumes) statistics for chloromethane (CAS. No. 74-87-3) in 1977 was between 100 and 500 million pounds. The Inventory gives ten producers at twelve sites for chloromethane production in 1977.[2]

In 1979, the Chemical Marketing Reporter (CMR) reported that U.S. production capacity was approximately 625 million pounds as produced by nine manufacturers at eleven sites (CMR 1979). The production volume in the United States averaged about 450 million pounds per year between 1970 and 1976, ranging from 544 million pounds in 1973 to 304 million pounds in 1975 (USITC 1970-1975). CMR reported that demand for chloromethane was 485 million pounds in 1978, 497 million pounds in 1979, and an estimated 550 million pounds in 1983, a growth rate of 2-3 percent per year through 1983, a result mainly of the growth potential of silicones (CMR 1979). The quantities of chloromethane that are either imported or exported are insignificant (Davis et al. 1977).

Chloromethane is used almost exclusively as an intermediate. Approximately 50 percent of all chloromethane is consumed in the manufacture of silicones which are used for a wide variety of products (CMR 1979). About 30 percent of chloromethane consumption is for the production of tetramethyllead, an antiknock compound used in gasoline formulations. This use is probably declining in the United States as a result of recent restrictions on the use of lead in gasoline, although tetramethyllead is being exported (CMR 1979).

[2]This production range information does not include any production/importation data claimed as confidential by the person(s) reporting for the TSCA Inventory, nor does it include any information which would compromise Confidential Business Information. The data submitted for the TSCA Inventory, including production range information, are subject to the limitations contained in the Inventory Reporting Regulations (40 CFR 710).

Minor uses of chloromethane as a methylating agent in the production of methyl cellulose, as an intermediate in the production of quaternary amines, and as an intermediate in the production of certain pesticides account for about 4 percent each of total consumption. A variety of other intermediate uses such as in the production of Triptane©, an antiknock fuel additive, and methyl mercaptan, used to produce jet fuel additives, account for about 4 percent of total consumption.

The major nonintermediate use of chloromethane, which accounts for about 4 percent of consumption, is as a catalyst-solvent in the manufacture of butyl rubber. Minor nonintermediate uses of chloromethane are as a foam-blowing agent for extruded polystyrene foams, e.g., Styrofoam^{R} (Shamel et al. 1975, NAS 1978, SRI Undated) and as a direct contact refrigerant (SRI 1979b). At one time chloromethane was used widely as a refrigerant in both domestic and industrial refrigerators. Although there are some refrigeration devices using chloromethane still in operation today, this use has been almost completely replaced by other substances, notably the chlorofluorocarbons. Chloromethane is also used as an aerosol propellant combined with dichloromethane, propane, and Freon 12 for various aerosol mixes (DeForest 1979).

B. Occupational Exposure

Because chloromethane is a gas at room temperature, the major route of human exposure to chloromethane is almost certainly inhalation. The 1972-74 National Occupational Hazard Survey (NOHS) indicates that an estimated 50,575 workers have the potential for exposure to chloromethane (NIOSH 1978). Although the chloromethane is stored, transferred, and reacted in relatively closed systems, the data discussed below indicate that chloromethane is present in the working environment and that significant human exposures do occur. Furthermore, elevated short-term exposure levels of chloromethane can occur through a leak or when operators must collect quality-control samples.

The National Institute for Occupational Safety and Health (NIOSH) has sponsored studies in several plants that produce or use chloromethane to evaluate the extent of worker exposure in various occupational settings. The exposure levels found in these studies, described below, were generally at or below the current threshold limit values (TLVs) for the time weighted average (TWA) as 100 ppm (210 mg/m^3) (weight/volume), the ceiling as 200 ppm, and the peak level (5 minutes in 3 hours) as 300 ppm (USOSHA 1974).

The American Conference of Governmental Industrial Hygienists (ACGIH) is proposing that the present TLV be lowered to 50 ppm, primarily on the basis of Repko's study discussed later (see Section III.B.2.) (ACGIH 1979).

At the Dow Corning plant site in Midland, Michigan, chloromethane is used in the production of methyl chlorosilanes in three buildings, and is used as a direct contact refrigerant in three other buildings (SRI 1979b). In the first industrial hygiene survey conducted by SRI International (SRI) at the Dow Corning Corporation on September 27, 1977 (SRI 1979b), it was determined that chloromethane levels in the working environment ranged from less than 1 ppm to 51 ppm (as area samples). In March 1979 SRI conducted a personal monitoring survey of the operators at the Dow Corning plant site for full shift TWA exposure concentrations. At least 38 operators work directly within areas of the plant that produce and use chloromethane. Additional workers with the potential for exposure include maintenance personnel, material handlers and laboratory personnel. Levels of chloromethane from below detection to 12.6 ppm were determined on operators, and short-term levels of 0.6 ppm to 5.8 ppm were determined on maintenance workers. Eight-hour TWA concentrations in four work areas were determined to range from below detection to 31.6 ppm. The highest levels were consistently found in chloromethane compressor areas. No samples were taken from areas in which chloromethane is used as a refrigerant.

Dow Chemical uses chloromethane as a foam-blowing agent in its polystyrene (Styrofoam^{R}) foam process (Crandall 1978, p. 2). The Styrofoam^{R} production occurs in a closed system until the material comes through a die in the extruder and expands onto a conveyer assembly. Employees are exposed to chloromethane in the foam production area. Exposure is also known to occur when chloromethane is liberated from the foam product while it is cooling and in storage, or when the residual chloromethane is released by certain operational procedures such as cutting, routing, drilling, and reaming of the finished product (Crandall 1978). Levels of 105 parts per trillion (ppt) (0.0001 ppm) and 355 ppt (0.00036 ppm) were found in two air samples collected from the foam storage warehouse (Crandall 1978, p. 12). The average eight-hour TWA exposure to chloromethane found in an SRI study ranged from 15 ppm to 54 ppm at various sites in the Styrofoam© plant, with the highest eight-hour TWA level being 101 ppm (Crandall 1978). In another SRI study, average half-hour concentrations at sample points in Dow's fabrication plants ranged from 2-1500 ppm (SRI Undated). In 1969 Dow Chemical conducted a survey of nine in-plant chloromethane-containing manufacturing operations using continuous monitoring devices for four months for 54 job classifications. Time weighted average concentrations ranged from 5-78 ppm with an average 30 ppm concentration. Peak concentrations were as high as 440 ppm, but the duration of peak concentration exposure was not reported (SRI Undated).

DuPont Corporation produces chloromethane and uses it in the production of tetramethyllead (SRI 1978a). Tetramethyllead is produced in a closed system by the reaction of chloromethane with a sodium-lead alloy and aluminum chloride. Unreacted chloromethane is pumped to a recovery unit. A concentration of 209 ppm was found in the tetramethyllead compressor room. In three operating areas where chloromethane is used, short-term levels ranging from undetectable to 71 ppm of chloromethane were found. Chloromethane exposure levels (as TWA) were 6 ppm to 57 ppm in the chloromethane manufacturing facility, 2 ppm to 75 ppm

in the tetramethyllead manufacturing facility, and 1 ppm to 34 ppm in the chloromethane recovery area. The duration of exposure to chloromethane for employees in the production area may be up to eight hours per work shift.

Continental Oil Company (Conoco) produces chloromethane with potential exposures in the production area and in the tank-car loading operations (SRI 1978b). In an industrial hygiene survey done by SRI at the Conoco Chemicals facility in Westlake, Louisiana, on October 18-19, 1977, it was determined from sampling data that chloromethane levels in the working environment ranged from 3 to 36 ppm (as area samples) (SRI 1979a). Simultaneous sampling by Conoco showed chloromethane concentrations ranging from less than 1 to 58 ppm. Personal sampling data accumulated by Conoco since 1975 in their quarterly sampling program showed eight-hour TWA chloromethane concentrations determined from personal monitoring varying from less than 0.2 to 7.5 ppm. Average eight-hour TWA concentrations in the air of 11 work aras ranged from 0.7 to 55.7 ppm. The highest concentrations were found in the compressor areas (SRI 1979a).

Chloromethane and methyl chlorosilane manufacturing facilities are located at a General Electric plant site (SRI 1978c). Workers were reported to be exposed to chloromethane levels of 0.8 ppm to 75 ppm in the manufacturing facility, recovery unit, and compressor room from three to five hours each day.

Chloromethane is also used in the manufacturing process of four herbicides: paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride); DSMA (disodium methylarsonate); MSMA (monosodium methylarsonate); and cacodylic acid (dimethylarsinic acid) (Sittig 1977). Paraquat is made by the reaction of 4,4'-bipyridyl and chloromethane in water. MSMA and DSMA are final products after sodium arsenite is treated with gaseous chloromethane. This reaction takes place in a closed system; additional chloromethane is consumed in a side reaction with sodium hydroxide.Inthe production of cacodylic acid,

chloromethane is added to the reaction chamber throughout the reaction, then the excess is bled off. No data were found on the occupational exposure to chloromethane in these four herbicide manufacturing processes, although the possibility of low-level constant air concentrations, or high-level intermittent concentrations exists, as in other manufacturing processes using chloromethane. No information was found on possible chloromethane contamination of these pesticides.

C. General Population Exposure[3]

Chloromethane appears to be the most abundant halocarbon present in the atmosphere (Lovelock 1975, Singh et al. 1977). With an average background tropospheric concentration of 611 ppt (0.0006 ppm) in the northern hemisphere, and 615 ppt (0.0006 ppm) in the southern hemisphere (SRI 1979c), the anthropogenic (i.e., those resulting from human activities) sources are relatively unimportant contributors to the atmosphere as extensive mixing probably does not occur in upper tropospheric levels. Lower stratospheric levels are approximately 5 percent less (Cronn et al. 1977).

Chloromethane is decomposed when it reacts with hydroxyl radicals in the troposphere, with a small fraction reaching the upper stratosphere, where it is destroyed by photolysis (NAS 1976). The National Academy of Sciences (NAS 1976) estimated that the residence time of chloromethane in the atmosphere is about one year. More recently, SRI (1979c) estimated the residence time in the atmosphere to be 231 days.

The National Academy of Sciences (1976) reported an estimated total global emission rate (both natural and anthropogenic

[3]Much of the information presented in this section is not necessarily directly relevant to EPA's analysis of the need to require health effects testing for chloromethane. However, this section is included to give an indication of the exposure of the population to chloromethane. The EPA is also evaluating the possible environmental effects of chloromethane, and the General Population Exposure subsection is applicable to that assessment as well..

emissions) of 14.7 billion pounds per year, based on an average global concentration of 750 ppt (0.00075 ppm). Two years later they estimated that the worldwide industrial emissions of chloromethane were 17.4 million pounds in 1973, only about 0.1 percent of the total emissions (NAS 1978).

The estimated intentional and unintentional U.S. chloromethane release to the atmosphere from its production, transport, storage, use, and presence as an impurity in other products, amounted to 11.4 million pounds in 1973, approximately 2 percent of the annual U.S. production volume (NAS 1978). Arthur D. Little, Inc. has similarly estimated that the United States produced approximately 60 percent of chloromethane worldwide in 1973 with an approximate release of 10.5 million pounds (Shamel et al. 1975 p. II-27 and p. III-21.)

If is is assumed that the 2 percent release rate applies worldwide, the total release of chloromethane would not exceed 20 million pounds. Using Singh et al.'s (1979) estimated 5-10 percent release rate from production, however, total release could be as high as over 50 million pounds annually. However, the chloromethane industry has calculated somewhat lower figures. Although, for example, Dow Corning vents escaping chloromethane from the manufacturing area through a stack to the outside air (SRI 1979b), the industry (NSF 1975) indicates that the fraction of total annual production escaping from the plant site to the atmosphere during manufacture of chloromethane is 0.0011-0.005 percent. In any case, industrial emissions of chloromethane appear to be only a small fraction of the total amount of chloromethane estimated to be entering the atmosphere annually.

It is believed that the oceans constitute a major natural source of chloromethane. Singh et al. (1979) reported that the average surface concentration of chloromethane in the Pacific Ocean is 26.8×10^{-9} g/liter (26.8 ppt). It has been suggested that iodomethane, found ubiquitously in ocean water, reacts with chloride ion in the ocean surface water to form chloromethane,

which then diffuses into the atmosphere (NAS 1976). Singh et al. (1979) have calculated that 6.6 billion pounds of chloromethane enters the atmosphere annually from the oceans.

It has also been suggested that burning vegetation is another important natural source of chloromethane. Palmer (1976) calculated that forest fires in the United States are responsible for about 252 million pounds per year of chloromethane released (average for 1972-1974). An additional 5.4 million pounds per year was calculated by Palmer to have been released from agricultural burning.

Another possible source of chloromethane is from photolytic decomposition of higher alkyl halides in the environment. The photolysis of gaseous chloroethane gives rise to chloromethane (Cremieux and Herman 1974), which suggests that levels in the atmosphere may be less static than is implied by the relatively long residence time estimated by either the National Academy of Sciences (1976) or SRI (1979c).

Although it is clear from the above information that major sources of atmospheric chloromethane are natural, anthropogenic sources may be responsible for significantly elevated local concentrations. For example, Singh et al. (1979) reported that they found elevated urban concentrations of chloromethane in Lisbon [2.20 parts per billion (ppb) (0.0022 ppm)] and near Los Angeles [average 1.50 ppb (0.0015 ppm); maximum 3.80 ppb (0.0038 ppm)]. They have suggested that automobile exhaust may be an important source of chloromethane. Palmer (1976) estimated that about 120 million pounds of chloromethane is released annually from building fires and 40 million pounds from the burning of polyvinyl chloride (PVC) in wastes (average for 1972-1974). The latter source was recognized by Palmer to be decreasing as the burning of such wastes was declining. The National Academy of Sciences (1978) estimated that tobacco smoking worldwide results in about 44 million pounds of chloromethane entering the atmosphere annually. Based on average human air intake of 23 m^3/day, and mean chloromethane concentrations over Los Angeles,

Phoenix, and Oakland of 3.00 ppb (0.003 ppm), 2.39 ppb (0.0024 ppm), and 1.07 ppb (0.0011 ppm), respectively, the average human dose of chloromethane was calculated to be 140 ug/day, 109 ug/day, and 60 ug/day at the three sites respectively (SRI 1979c).

Elevated levels of chloromethane can occur in indoor air. Measurements of chloromethane in various contained atmospheres showed between 0.65 ppb (0.00065 ppm) and 8.00 ppb (0.008 ppm) by volume in various automobiles, 1.4 ppb (0.0014 ppm) in a restaurant, and over 20 ppb (0.02 ppm) in an apartment after a cigarette was smoked (Harsch 1977). Chloromethane was generally the predominant halomethane found in indoor air and was typically present at between two and ten times the ambient outdoor level (Harsch 1977, NAS 1978). It was suggested by the National Academy of Sciences (1978) that these elevated indoor levels may be due to cigarette smoking.

Chloromethane is found primarily in the air and ocean surface water, although it has also been qualitatively detected once in United States river water, three times in effluents from chemical plants, twice in effluents from sewage treatment plants, and eight times in drinking water (ORD 1979), very possibly from the chlorination of drinking water (Davis 1977, USEPA 1979c). The total number of times tested was not indicated. For the protection of human health from the toxic properties of chloromethane ingested through water and through contaminated aquatic organisms, the ambient water criterion level for chloromethane is 2 ug/l (USEPA 1979c).

Although chloromethane is present in the atmosphere at a background parts per trillion level from natural sources (e.g., ocean waters) and at a parts per billion level in urban atmospheres from anthropogenic (e.g., cigarette smoke) sources, the EPA believes that the local, high concentrations of chloromethane in the parts per million levels found in occupational settings present the greatest risk of health effects resulting from exposure to chloromethane.

III. Health Effects

A. Systemic Effects

1. Data Evaluation

a. Human Studies

The EPA is not aware of any epidemiology study which evaluates the systemic effects of chloromethane in humans exposed chronically. However, there is a substantial case history literature of poisoning in humans, beginning with Gerbis' paper in 1914. Smith and von Oettingen (1947a) tallied the number of published chloromethane intoxication cases. By 1947 there were 210 reported cases, of which 15 were fatal. The majority of poisonings before 1960 were due to exposure from chloromethane's use as a refrigerant (see e.g., Kegel et al. 1929, Schwarz 1926), while present day poisonings in this country appear to occur mainly in the rubber and plastics industries (see e.g., MacDonald 1964, Scharnweber et al. 1974).

Most of the case histories are believed to have involved acute exposures to levels of the chemical well in excess of the current TLV of 100 ppm (see e.g., Gerbis 1914, Kegel et al. 1929, Laskowski et al. 1976, Schwarz 1926) although idiosyncratic responses to low levels could conceivably account for some known instances of toxicity. In mild cases of acute poisoning, the toxic manifestations are primarily neurologic in character, as are those in chronic intoxications (see Section III.B.). However, gastrointestinal effects such as nausea, vomiting, and diarrhea are also common (see e.g., Mackie 1961, Sharp 1930, van Raalte and van Velzen 1945, Wiernikowski et al. 1974). Elevated body temperatures, pulse rate and heart rate are frequently reported (see e.g., Hansen et al. 1953, Kegel et al. 1929, Laskowski et al. 1976), while depressed blood pressure (see e.g., McNally 1946, Suntych 1956, Trubecka and Brzeski 1968, Weinstein 1937), and abnormal EKG readings (see e.g., Gaultier et al. 1965, Gummert 1961, Noro and Pettersson 1960, Walter and Weiss 1951) also indicate cardiovascular involvement.

The other organs or systems primarily influenced by chloromethane are the liver, kidney, and blood. Hepatic injury occurs in acute cases (see e.g., Saita 1959, Spevak et al. 1976, Weinstein 1937), and in long-term exposures (see e.g., Del Zotti and Gillardi 1954, Mackie 1961, Wood 1951), while kidney damage manifests itself as renal insufficiency and anuria in the more severe cases (see e.g., Borghetti and Gobbato 1969, Hayhurst and Greenburg 1929, Kegel et al. 1929, Suntych 1956) and proteinuria in less severe cases (see e.g., Birch 1935, Mackie 1961, McNally 1946).

The hematologic picture is not as clear. Although some investigators have seen anemia (see e.g., Hayhurst and Greenburg 1929, Kegel et al. 1929, Mackie 1961) and others leukocytosis (see e.g., McNally 1946, Noro and Pettersson 1960, Suntych 1956, Wiernikowski 1974), in other instances the blood cell counts remain within normal levels following severe poisonings (see e.g., MacDonald 1964, Spevak 1976, van Raalte and van Velzen 1945, Weinstein 1937).

Although most exposures to chloromethane are assumed to be by inhalation, the lung appears to be relatively insensitive to the chemical.

b. Animal Studies

There have been few studies on the effect of repeated exposure to chloromethane in animals. Details of four of the most relevant of these studies follow.

An experiment was undertaken by White and Somers (1931) for the purpose of determining the minimal concentration of chloromethane which would cause death in average-sized guinea pigs when the exposure via inhalation covered a 72 hour period. After the exposure period, the animals were observed for an additional thirty days. Each of three groups of animals (18 animals per group) was exposed to an average concentration of 49, 77, or 140 ppm. In the group exposed to an average of 49 ppm, none of the animals died within the 30 day observation period; in the group

exposed to an average of 77 ppm, 50 percent of the guinea pigs died; and in the group exposed to an average of 140 ppm, all of the animals died within a few days after exposure. The pathologic changes in the guinea pigs dying from the effects of chloromethane indicated widespread systemic poisoning characterized mainly by severe circulatory disturbances and congestion of the lungs and meninges.

The acute and chronic toxicity of chloromethane have been studied (Smith and von Oettingen 1947a,b, Smith 1947, Dunn and Smith 1947): the mortality, symptomatology, effects on hematopoietic and biochemical parameters, and the histopathologic changes resulting from exposure. In these studies, the chemical was administerd to 10 species of animals via inhalation 6 hours/day, 6 days/week for up to 64 weeks, at concentrations of 300-4000 ppm.

Table 2 summarizes the mortality data at 500 and 2000 ppm in terms of the number of days from first exposure to death of 50 percent of the experimental animals (LT50) (Smith and von Oettingen 1947a). The most sensitive species at the 500 ppm concentration was the dog; the least sensitive was the rat. No apparent effect was noted in guinea pigs, mice, dogs, monkeys, rabbits, and rats exposed to 300 ppm, 6 hours/day, 6 days/week for 64 weeks. The other four species were not exposed to this concentration.

TABLE 2

Mortality of Animals Exposed to Chloromethane
6 Hours/Day, 6 Days/Week
LT50 (Days)

Species	500 ppm	2000 ppm
Guinea pig	71	3
Mouse	143	3
Goat	NS[a]	3
Dog	23	4
Monkey	110	10
Rat	NE[b]	15
Rabbit	192	23
Cat	NS	27
Chicken	NS	38
Frog	NE	NE

[a]NS--not studied
[b]NE--not lethal

Smith and von Oettingen (1947a) also found that several factors influenced survival time within a species. These factors included exposure frequency, age, and certain dietary constituents. As shown in Table 3, the interval between exposures (i.e., exposure-free period) greatly influenced the mortality rate. Allowing exposure-free periods may decrease the cumulative effects of chloromethane. The work of White and Somers (1931) also indirectly supports this hypothesis. In their study, the LD_{50} for guinea pigs exposed to chloromethane continuously for 72 hours was only 77 ppm, indicating that uninterrupted contact is much more lethal.

TABLE 3

Mortality of Animals Exposed to Chloromethane for Different Exposure Intervals

Species	Concentration (ppm)	Exposure Time (hours/day)	Frequency (days/week)	LT50 (days)
Mouse	1,000	6	6	5
	2,000	3	6	131
	2,000	6	6	3
Guinea	2,000	6	6	3
Pig	2,000	6	3[a]	201

[a]Three alternate days a week

Variation in age also influenced mortality. Younger animals appeared to be more resistant than older animals. For example, when adult and weanling rats were exposed to 2000 ppm, 6 hours/day, 6 days/week, the LT50 for the adult animals was 15 days, while that for the weanlings was 27 days.

Supplementing the diet of guinea pigs exposed to 1000 ppm with ascorbic acid, or the diet of rats exposed to 2000 ppm with thiamine hydrochloride, nicotinic acid, or calcium pantothenate did not increase resistance to the lethal effects of chloromethane. However, increasing dietary casein by 20 to 35 percent or supplementing moderate to low casein diets with cystine or methionine led to an increase in the time before 50 percent of the rats died.

No differences in LT50 could be attributed to differences in sex.

Smith and von Oettingen (1947b) also studied the symptomatology of the animals poisoned by chloromethane. Commonly seen were anorexia, discharge of fluid from the respiratory tract, hyperactive reflexes, disturbances in ability to correct position, and extreme spasticity. The neurologic behavior of monkeys (tonic-clonic convulsions and periods of unconsciousness), was different from that of dogs (sustained tonic spasms

without remission). However, both types of neurotoxicity have been reported in humans (see Section III.B.).

Development of toxicity signs varied with concentration and frequency of exposure: delayed or gradual with low concentrations or, with high concentrations, separated by longer exposure-free intervals. Young animals responded with a slow development at some concentrations where older animals developed symptoms acutely. Although animals generally recovered from acute symptoms if exposure was discontinued when symptoms first appeared, effects acquired over a long period of time were sometimes irreversible.

Smith (1947) reported hematologic and biochemical results on certain of the animals studied by Smith and von Oettingen (1947a,b). No hematologic or biochemical test was purported to be useful in the diagnosis of chloromethane poisoning in the species studied. No evidence of liver dysfunction, renal failure, or of a primary effect upon the formed elements of the blood were detected without severe neuromuscular disturbances having preceded the detected hematologic or biochemical changes. These data indicate the CNS to be the system most sensitive to chloromethane toxicity.

Histopathologic examination of the same group of experimental animals was reported by Dunn and Smith (1947). Morphologic changes that appeared to be a direct result of inhalation of chloromethane 6 hours/day, 6 days/week, for 9 months were variable degrees of necrosis of the convoluted tubules of the kidney in mice and rats (2,000 ppm) and fatty metamorphosis of the liver in the smaller species. Pulmonary edema appeared to be a direct result of the irritation due to inhalation of chloromethane. No morphologic changes were found in the brains of those dogs and monkeys examined which showed severe neuromuscular disturbances. No morphologic changes were observed in the rats exposed to 500 or 1000 ppm, 6 hours/day, 6 days/week for nine months. However, the tissues examined were not specified. Guinea pigs surviving 9 months of exposure at 500 ppm also

demonstrated no histopathologic changes, although guinea pigs were the second most sensitive species (LT50) at 500 ppm while rats showed no lethality at 500 or 1000 ppm (Smith and von Oettingen 1947a).

The major limitations of the four studies done by Smith, von Oettingen, and Dunn are:

(1) small numbers of animals were used in certain test groups (e.g., two goats at 2000 ppm, four rabbits at 1000 ppm, two monkeys at 500 ppm);

(2) histopathologic examinations were not reported on animals exposed to 300 ppm for 64 weeks for species which showed effects at 500 ppm; and

(3) no indication of the animals or tissues routinely examined was given.

Therefore, while the studies indicate at what levels major effects of concern might appear, they are insufficient for determining more subtle adverse effects detectable at the present state of the art.

Yevtushenko (1966) studied the chronic effects of chloromethane on rats (10 animals/group) and rabbits (4 animals/group), exposed to 40 or 240 mg/m^3 (i.e., approximately 20 and 120 ppm, respectively), 4 hours/day, daily for 6 months. In both groups of rats hematologic examination revealed consistent decreases in erythrocyte number. In both rats and rabbits exposed to 240 mg/m^3, excretory function of the liver was disturbed while no effect was observed in the animals exposed to 40 mg/m^3. In rats of both groups, kidneys functioned normally, but microscopic examination of the blood-forming organs indicated depletion of lymphoid elements and proliferation of the reticular base of the organs examined (spleen, lymph nodes). Changes in parenchymal tissues were unpronounced. The rabbits were also used to examine effects on the eyes. These were observed in both exposure groups

and included discoloration of the optic disc and histopathologic disturbances of the retina and optic nerve. The most significant changes occurred in the CNS (see Section III.B.).

CIIT has sponsored a 90-day inhalation study using rats and mice performed by Battelle Laboratories (1979). Groups of animals (10 animals/sex/dose) were exposed to 375, 750, or 1500 ppm of chloromethane 6 hours/day, 5 days/week for 13 weeks. All three groups of treated male rats showed a significant decrement in body weight compared to controls, while female rats treated with 750 and 1500 ppm also showed significant decrements in body weight compared to controls. There was a significant difference in final body weight between treated and control mice only at the 1500 ppm dose level in females, however. No clinical signs of toxicity or overt behavioural changes were noted during the study. The group of male mice treated with 1500 ppm had significantly higher serum glutamic-pyruvic transaminase (SGPT) activity than controls. However, this activity was increased in only two of the mice. One was found to have a liver infarction while the other had severe hepatic changes. Other clinical and hemotologic parameters measured were reported to be within the normal clinical range. The major histopathologic finding was cytoplasmic vacuolar changes of the hepatocytes in mice. Sixty-four percent (9/14) of the mice treated with 1500 ppm exhibited this effect, 39 percent in the 750 ppm group, and 37 percent of controls. The effect was highest in females in all groups. One female not in the high dose group had a massive liver infarction. Thirteen of the 60 treated mice had eye lesions which were reported to be compound related.

However, deficiencies in the design and conduct of this study, have led the EPA to decide that the findings from it cannot be used as the sole determinant of the chronic toxicity of chloromethane:

(1) The rat does not appear to be the most appropriate test species for systemic chronic effects at the dose levels used. This species was previously shown to be unaffected by exposure to 1000 ppm chloromethane, 6/hours/day, 6 days/week for 64 weeks (Smith and von Oettingen 1947 a,b). Also, since the toxicity of chloromethane decreases as the exposure-free period is increased, one would anticipate that decreasing the exposure frequency to 5 days/week over 90 days would lead to little, if any, toxicity even at 1500 ppm. Dogs or monkeys may be more appropriate since they showed signs of toxicity even at 500 ppm, 6 hours/day, 6 days/week and exhibited neurologic and behavioral effects seen in humans exposed to chloromethane (Smith and von Oettingen 1947a, Smith 1947).

(2) Of the 80 mice used in the study, 19 died during the 13-week study; 14 of which died due to stated problems with new cages. Seven of those dying of trauma were in the high dose group of male mice.

(3) There was a wide range of response in the control groups. A large standard deviation in a control group means that the difference between a treated group and the control group needs to be larger in order to detect a significant difference. Therefore, in a better controlled study, perhaps more significant differences would have been detected.

Also in progress at the contract laboratory, CIIT has sponsored a 24-month chronic inhalation study in mice and rats. This study was initiated in June 1978; to date, the EPA has received a 6 month interim report (Mitchell et al. 1979). The exposure levels being administered are 50, 225, and 1000 ppm. The frequency of administration is 6 hours/day, 5 days/week for

24 months. As originally planned, during the last 6 months of the study, the animals would not be exposed to chloromethane but would be held for observation. CIIT has chosen to extend the dosing period to the full 24 months. There are 120 animals of each sex in each of the three exposure groups and in each of two control groups. Interim sacrifices are scheduled at 6, 12, and 18 months. In the interim report submitted to the EPA (Mitchell et al. (1979), it was revealed that female mice in all treated groups and male mice treated with 1000 ppm showed significant body weight decrements compared to controls. This is in contrast to the results reported in the 90-day probe study. Chronic inhalation of chloromethane in the interim-sacrificed mice (1000 ppm) was reported to be associated with focal acute scleritis (3/10 males, 1/10 females), hepatocellular degeneration (7/10 males, 7/10 females), splenic lymphoid depletion (8/10 males, 4/10 females) and thymic lymphoid necrosis (4/10 males, 1/10 females). In rats chronic administration of the chemical was reported to be associated with sperm granuloma (2/10), interstitial pneumonia (1/10 males, 4/10 females) and subacute tracheitis in females (5/10). No significant histopathologic findings were discovered in the liver of rats or in the kidneys of rats or mice.

2. Current and Planned Testing

The Chemical Industry Institute of Toxicology (CIIT) has in progress a toxicologic evaluation of chloromethane in laboratory animals. The major components of the CIIT program are a pharmacokinetics study, a 90-day preliminary study, teratogenesis-reproduction studies, and a 24-month chronic inhalation toxicity study.

The 90-day probe study performed by Battelle (1979), involved the inhalation exposure of F-344 albino rats and $B_6C_3F_1$ hybrid mice to various levels (300, 750, 1500 ppm) of chloromethane, 6 hours per day, 5 days per week for 13 weeks. Results from this study are discussed in Section III.A.I.. The purpose of this study was to select appropriate exposure levels

for the subsequent long-term toxicity study. However, in the 90-day study (Battelle 1979), there was no significant weight decrement in treated male mice even at 1500 ppm, while female mice showed such a decrement only at 1500 ppm. In contrast, in the 6-month interim report of the 24-month study, weight loss has been recorded in all groups of treated female mice. The EPA believes that in a chronic/oncogenicity study, the lowest dose should represent a level demonstrating no toxicity at such an early stage, even weight loss.

The 24-month toxicity study was initiated by CIIT's contractor in June 1978, and a six-month interim report has been received by the EPA. A memorandum from CIIT (Gralla 1979) has raised various questions about the conduct of the study as reported, which the Agency finds of concern. For instance, in the six-month interim report, CIIT reported a significant death rate due to trauma, especially within the first 6 months in male mice. There was an overall death rate due to trauma of 4.5 percent. For male mice this rate was almost 9 percent. CIIT has informed the EPA that the number of male mice reached a critically low level, at which time (22-months) they were sacrificed. This high death rate due to trauma indicates concern that good laboratory practices are not always followed.

Regarding chronic toxicity specifically, various factors potentially will affect the usefulness of the results:

(1) As discussed previously in Section III.A.1., the protocol calls for exposing rats to dose levels which previously have been shown to cause no effects on the liver, kidney, cardiovascular or hematopoietic systems of rats.

(2) Because a non-rodent, the dog, appears to be the species most sensitive to chloromethane, the use of two rodent species may give spurious no-effect levels when used to evaluate the risk to humans.

(3) No tests will be conducted to determine the more discriminating aspects of behavior and performance.

3. Conclusions

Several major conclusions about the chronic toxicity of chloromethane can be drawn from the human studies and from the animal studies of White and Somers (1931), Smith and von Oettingen (1947a, b), Smith (1947), Dunn and Smith (1947), Yevtushenko (1966), and CIIT (1979a). These conclusions are:

(1) chloromethane is toxic to a variety of species including humans;

(2) the major systems affected include the CNS, liver, kidney, blood forming elements, and ocular tissue;

(3) the most sensitive system affected in humans and animals appears to be the CNS; and

(4) the level of toxicity is not only affected by the exposure concentration but also by the length of the exposure-free period and the amount of cystine or methionine in the diet.

4. Testing

Although the Interagency Testing Committee (ITC) recommended testing to determine chronic effects on the liver, kidneys, bone marrow, and cardiovascular system, the EPA is not proposing such studies. Results available from previous studies, especially those of Smith and von Oettingen (1947a,b), Smith (1947), Dunn and Smith (1947), Yevtushenko (1966), Battelle (1979) and that which will be available from the current CIIT study (CIIT 1977) are deemed by the Agency to provide sufficient information to evaluate the chronic effects of chloromethane on the liver, kidney, bone marrow, and cardiovascular system. In the earlier studies the liver, kidneys, and bone marrow were affected, but at

exposure levels higher than those that induced CNS effects. This means that no-effect levels were in essence established for liver, kidney, and bone marrow toxicity. The no-effect levels varied with the frequency of exposure. For example, in rats exposed to 500 ppm, 6 hours per day, 6 days per week for nine months, no signs of liver, kidney, or bone marrow toxicity were detected (Dunn and Smith 1947), while exposure to less than 120 ppm was needed if the exposure frequency was 4 hours/day daily for 6 months (Yevtushenko 1966). Because no-effect levels have been determined for liver, kidney, and bone marrow toxicity under a series of test conditions, the EPA finds that no further chronic toxicity study to examine these systems is needed.

Effects on the cardiovascular system are associated with acute lethal concentrations of the chemical and not with non-lethal chronic exposure. Human and animal data already available are sufficient to evaluate the acute toxicity of chloromethane. Because of these two factors the EPA is not proposing further chronic studies to evaluate cardiovascular toxicity.

B. Neurotoxicity

1. Data Evaluation

a. Acute Effects

i. Human Studies

There have been numerous human case reports of acute intoxication (see e.g., Noro and Pettersson 1960, Spevak et al. 1976, Thordarson et al. 1965, Wiernikowski et al. 1974). The first column of Table 4 shows the frequency and nature of reported signs and symptoms. Neurologic signs include ataxia, tremor, motor reflex changes, and signs of cranial nerve involvement such as blurred vision, weakened convergence, mydriasis, and vertigo. Mood changes such as apathy, irritability, euphoria in earlier stages of acute exposure and/or depression in later stages also occur. Cognitive deficits relate to difficulties in concentration and memory loss. More severe CNS alterations also occur in acute poisoning. Convulsions of both the tonic-clonic type (Hartman et al. 1955, McNally 1946) and that characterized

Table 4. Neurologic Symptoms Seen in Man

References	Kegel et al. (1929) (7)[a]	Weinstein (1937) (2)	van Raalte & van Velzen (1945) (1)	McNally (1946) (8)	Noro and Pettersson (1960) (5)	Wiernikowsky et al. (1974) (3)	Spevak et al. (1976) (4)	Baker (1927) (21)	Sharp (1930) (2)	Hansen et al. (1953) (15)	Mackie (1961) (1)	MacDonald (1964) (8)	Scharnweber et al. (1974) (6)	Anon. (1945) (1)	Langauer-Lewowicka et al. (1974) (25)
Clinical Symptoms															
visual disturbances	5[b]		1	2	+[c]	+		16		6	1	5	3		2
diplopia	1				+		2	4					2		3
ptosis	2							21							+
mydriasis	6			2			4								
anisocoria				2			4								5
nystagmus	1						4								
weakened convergence							2								3
strabismus	1						2								
photophobia							4								
dysphagia								3		2			1		
hiccup	3				+			1		2					
paresis of facial nerve			1				4								3
twitching muscles	3		1				4							1	
tremors	2		1	1		+	4	5	1				1		3
pyramidal signs						+	4								17

Table 4. Continued

References	Kegel et al. (1929) (7)	Weinstein (1937) (2)	van Raalte & van Velzen (1945) (1)	McNally (1946) (8)	Noro and Pettersson (1960) (5)	Wiernikowsky et al. (1974) (3)	Spevak et al. (1976) (4)	Baker (1927) (21)	Sharp (1930) (2)	Hansen et al. (1953) (15)	Mackie (1961) (1)	MacDonald (1964) (8)	Scharnweber et al. (1974) (6)	Anon. (1945) (1)	Langauer-Lewowicka et al. (1974) (25)
Clinical Symptoms															
ataxia	2		1							8			1		
Rombergism			1				4								
vertigo	1	2						21				1	1		+
staggers			1					21		2		6	3		
loss of balance													1		+
dizziness	1		1			+			1	12		8	2	1	+
adiadochokinesis							1								
paresthesia			1												+
sensitivity							3								+
weakness in limbs				2	+								1		3
generalized weakness	4		1	1	+					9	1	3		1	+
apathy							1				1				
tiredness, sleepiness	5		1				4	21		12		1	1		+
euphoria							2					1			
depression			1									4			

Table 4. Continued

References / Clinical Symptoms	Kegel et al. (1929) (7)	Weinstein (1937) (2)	van Raalte & van Velzen (1945) (1)	McNally (1946) (8)	Noro and Pettersson (1960) (5)	Wiernikowsky et al. (1974) (3)	Spevak et al. (1976) (4)	Baker (1927) (21)	Sharp (1930) (2)	Hansen et al. (1953) (15)	Mackie (1961) (1)	MacDonald (1964) (8)	Scharnweber et al. (1974) (6)	Anon. (1945) (1)	Langauer-Lewowicka et al. (1974) (25)
confusion	2				+					1		4	2		
nervous, worried	1									1		2	3		
irritable												2			
loss of memory	1					+				1		1	3	1	+
loss of libido											1	1			
psychosis															2
insomnia	1		1					15							
anorexia	1		1					21		1	1				
nausea	5	2	1	1	+			11	2	5	1	6		1	
speech disturbance	2		1			+	4			3		2	4		
headaches	2				+	+				1	1	7	1		+
hearing difficulties						+									
difficulty in concentration	1					+				1			1		
heavy head	1											2			
convulsions	2			1											

a) The number in parentheses following the year of the reference is the number of persons exhibiting chloromethane intoxication in the paper.
b) The number of patients exhibiting this particular sign.
c) If the number of persons exhibiting the sign was not mentioned, but the sign was reported as occurring, a (+) is indicated.

by sustained tonic contractures (Kegel el al. 1929, Schwarz 1926) have been seen. Other major symptoms are headache, fatigue, and sleep disturbances. The onset of these signs and symptoms may be delayed by several hours following exposure, and they can persist indefinitely following cessation of exposure (see e.g., Gudmundsson 1977, Walter and Weiss 1951). These studies generally lack any quantitative estimates of levels or duration of exposure, which makes them difficult to use as more than suggestive evidence.

Although victims of acute exposure usually show complete and rapid recovery, very long lasting changes have also been reported. Gudmundsson (1977) did a follow-up study 13 years after 15 people were exposed to chloromethane from a leaking refrigerator on a fishing boat (Thordarson et al. 1965). One patient died within 24 hours of the incident, two suffered severe depression and committed suicide within 2 years of the incident, and one man who had been seriously disabled, died ten years later of a coronary occlusion. Ten of the eleven survivors were examined. Nine patients reported a reduced tolerance to alcohol and six had chronic fatigue and depression. Five patients showed neurologic signs: 3 with tremor, 2 with paralysis of accommodation, and 2 with peripheral neuropathies complicated, however, by a history of alcohol abuse. Hartman et al. (1955) reported that 1.5 years following a severe acute exposure, a woman still displayed intention tremor, headaches, insomnia, and "nervousness". Few of the other studies in the literature have reported any long term follow-up.

There have been 2 recent laboratory studies of acute exposure in humans. Putz et al. (1979) reported behavioral performance deficits in a complex visual vigilance task during and after 3 hours of exposure to 200 ppm, but no effects at 100 ppm. Stewart et al. (1977) exposed 4 humans to 100 ppm for 5 days for 7.5 hours a day. Analysis by the authors revealed no impairment on a battery of neurologic and behavioral tests, including 2 timing tasks, one with no cues and one with auditory

cues. However, their analysis of variance revealed a significant impairment in a timing task that relied on visual cues. Although the investigators concluded that there was no cognitive impairment of timing behavior, the EPA believes that the demonstration of a visual system-related decrement in such a controlled study seems significant when considered in light of Putz's visual task deficits after 3 hours at 200 ppm.

ii. Animal Studies

Yevtushenko (1966) reported that the four hour LC_{50} (lethal concentration in 50 percent of the animals) for rats was roughly 11,000 ppm. Depression of motor activity occurred, as well as widespread edema and vascular congestion of the brain and other organs. A four hour exposure to 114 ppm was reported to produce a behavioral deficit, namely, an increase in the time required to develop a conditioned reflex.

b. Subchronic and Chronic Effects

i. Human Studies

Based on a study of refrigeration workers, Klimkova-Deutschova (1957) suggested that fatigue, headache, sleep disturbances, and difficulty in concentration are among the earliest symptoms of chronic intoxication, that cerebellar neurologic signs predominate early, but that extrapyramidal signs are more frequent with a later onset. In addition, onset of toxicity was insidious and once signs and symptoms appeared they were sometimes permanent.

In many reports it appears that signs and symptoms were reported in workers exposed both chronically at low levels and acutely at much higher levels from accidental spills or leaks (see e.g., Baker 1927, MacDonald 1964, Scharnweber et al. 1974; see also the second column of Table 4). This makes these studies difficult to evaluate in relation to separating chronic from acute effects. As in acute case reports, quantitative exposure data or correlation with employment duration are generally absent for both mixed and chronic exposure studies.

Belova and Yevtushenko (1967) performed detailed examinations of the visual system of chronically exposed workers. In those exposed to chloromethane for 2 to 3 years, roughly one-third showed a decline in corneal sensitivity and in some there was slight discoloration of the optic disc. Two-thirds of those exposed for 5 to 8 years showed a decline in corneal sensitivity. In addition, half of the workers displayed a complex group of visual changes. Although age-related deficiencies were apparently not factored out, the authors felt that these ocular problems were related to exposure to the chemical.

Repko et al. (1976) performed a behavioral, neurologic, and psychological study of chronically exposed workers (1-311 months, mean=84 months) in comparison with a control group. This study, performed for NIOSH, may be indicative of neurobehavioral effects in workers exposed long-term to low levels of chloromethane. However, the data could also be interpreted to mean that acute exposures to low levels of chloromethane adversely affect those tested. Additional defects in the test, listed below, reduce the effectiveness of such conclusions and leave the results open to question.

The exposed cases consisted of 171 "physically normal" paid volunteers from eight different plants at seven locations in six states (11 female/160 male, 10 black or minority/161 white). The controls (comparisons), who were matched (attempted) by sex, age, and race to the cases, consisted of 49 workers who were not known to be exposed to chloromethane or other neurotoxicants (3 female/46 male, 3 black or minority/46 white). Regardless of matching, the differences in mean age and level of education between cases and controls were statistically significant. These differences, and the case selection procedure (paid volunteers), as well as "physically normal" persons, may enter bias into the study, as a random sampling is the preferred type of selection. There were also serious problems with the time sequence of exposure and effect measurements in the study. Behavioral

testing, performance measurements and urine samples were taken among the workers in groups of five, three times a day, at times corresponding to the end of eight-hour work days. Alveolar breath samples of chloromethane were taken immediately before the end of this eight-hour work day. The following day, neurologic and EEG examinations were performed, and blood samples were collected. No mention was made of quality control for the behavioral, neurologic and EEG testing. During the period in which these examinations were conducted, ambient concentrations of chloromethane were determined for the various work locations (2-70 ppm, mean=34 ppm). This short-term sampling does not estimate long-term chronic exposure. However, Repko et al. state: "most of the information for subject exposures to methyl chloride vapors obtained by short-term air sampling techniques correlated well with the information obtained by the permanently installed monitoring instrumentation"(p. 104). Nevertheless, these ambient air measurements do not quantify chronic exposure, because the duration of each individual's exposure to chloromethane was not considered in most analyses.

The data analysis performed by Repko et al. to determine this relationship exemplifies the limitations of the study. Overall, the statistical comparisons are not sensitive to cumulative exposure simply because this information is not contained within the data. However, an attempt was made to establish a relationship between duration of chloromethane exposure (months employed) and physiologic effects of exposure. Duration of exposure was compared with measurements of breath chloromethane, urine pH, hematocrit, and ambient air concentrations of chloromethane. A statistically significant positive correlation was found between breath and air levels, and a negative correlation was found between air concentration and hematocrit levels. In subsequent analyses, correlations between neurologic effects and these physiologic variables were investigated. For the behavioral data, means from cases and controls were compared. Such a technique does not distinguish levels of exposure among cases. Behavioral data were

investigated via scatter plots of ambient air concentration versus factors related to behavioral tasks. This comparison investigates the responses to various doses measured in the workplace. Repko et al. (1976) concluded that performance levels were reduced among workers exposed to chloromethane. Due to the aforementioned limitations of the study design, this reduction is only suggested rather than conclusively supported. No measurements of performance previous to exposure (pre-employment) were obtained. Therefore, there is no certain means of knowing whether or to what extent the workers' performance levels were affected by exposure.

Therefore, although Repko et al. found a significant decrement among the workers in complex math tasks, increases in the latency of responses to visual stimuli, and increases in resting tremor, a relationship between these effects and chloromethane levels could only be suggested because of these methodological problems.

ii. Animal Studies

As noted above, the major study of chronic toxicity in animals (rats, mice, guinea pigs, rabbits, dogs, monkeys, others) was performed by Smith and von Oettingen (1947a,b) (see also Section III.A.). Neurologic effects seen in the 500, 1000 and 2000 ppm groups exposed for 6 hours/day, 6 days/week are summarized in Table 5. In general, they found that 300 ppm for 64 weeks "had no apparent effect on any species tested", but that 500 ppm produced serious toxicity in most species, with particularly pronounced neurologic signs in dogs and mice.

A Russian study (Yevtushenko 1966), which the author cited as one basis for the 1965 Soviet TLV of 2.5 ppm, reported behavioral and pathologic effects in rats and rabbits exposed for 4 hours/day to either 120 ppm or 20 ppm for 6 months. Development time for a food conditioned reflex to a bell increased in both groups of exposed rats compared to controls, while the unconditioned reflex to the sight and smell of food was significantly delayed in rats exposed to 240 mg/m^3. Microscopic examination

Table 5. Neurologic Signs Occurring Following Continued Exposures

Air Concentration in ppm	Species	Effects
500	Mice	Convulsive activity occasionally occurred during the first week. After a week or more of exposure, mice developed a syndrome which began with a clamping of the hind legs to the body when the mouse was held up by the tail. This syndrome worsened with continuing exposure. Mice surviving 15 weeks of exposures retained the clamping response 6 months following termination of exposure.
	Dogs	Three of four dogs exhibited spasticity and staggering by the end of the second week. Two days later two were no longer able to stand and the third was shaking violently. Two died within the next 8 days and the third showed maximum extensor rigidity and opisthotonus when it was held off the floor. The fourth animal developed a slight ataxia after 4 weeks, lack of neuromuscular fine control following 2 months exposures, prominent tremors, ataxic gait and abducted hind legs when standing at 6 months. Tendon reflexes were hyperactive and spasticity increased when the dog was lifted off the floor. Exposures were discontinued after 29 weeks, and during the following 17 weeks there was no notable amelioration of the neuromuscular symptoms.
1,000	Guinea Pigs	Loss of righting reflex; hind leg displacement reflex retarded; later development of convulsions and opisthotonus within the first week. Following exposure to 3 weeks of chloromethane, neuromuscular signs first appeared and progressed until the guinea pig was unable to walk. At 12 weeks a regular flicking of the ears and a fine tremor was noticeable, but running a pencil along the mesh of the cage would initiate a convulsive episode. At 14 months, although many neuromuscular effects had disappeared, it still could not right itself.
	Dogs	Generalized tonic spasm with powerful opisthotonus and risus sardonicus; hyperactive reflexes and coarse tremors accompanied spasticity occasionally in the first week of exposure.

Table 5. Continued

Air Concentration in ppm	Species	Effects
	Puppies	First symptoms appeared in second month of exposure when alternate gait was replaced with gamboling gait with frequent tumbling. In the third month the more severely affected pup showed tremors, and after 11 weeks intermittent convulsive seizures, attacks of hiccups, audible grinding of the jaws and risus sardonicus, and sustained contraction of tongue and jaw muscles. Exposures were discontinued at 12 weeks, and the general condition of the more severely affected animal improved for about one month, but after the fourth month, it grew worse and was sacrificed three months later. The other pup was observed for 10 1/2 months and the general condition was excellent, though the pup could not stand without sagging or swaying of the posterior trunk and legs and there was a tendency for the hind legs to remain displaced posteriorly.
	Rabbits	After several weeks exposure to chloromethane rabbits were first unable to bring the hind legs to the normal position for hopping, and later the hind legs gradually became permanently adducted.
2,000	Chickens	After three weeks the legs became weak and abducted and the chickens unable to walk. Debility and paralysis increased until the entire body except head and neck were paralyzed and cold to touch.
	Cats	After a week, cats became weak, ataxic, lost righting reflex. Symptoms progressed until cats unable to walk and had frequent extensor spasm. Hyperactive reflexes.
	Rats	Rats on stock diet occasionally showed opisthotonus. On semi-synthetic diet, in which survival times were prolonged, the clamping syndrome seen in mice appeared after about 5 weeks of exposure, culminating in paralysis of the hind legs several weeks later. Residual abnormalities observed after 4 months in one rat.
	Goat	Following removal from the exposure chamber after the fourth exposure, the legs became rigidly extended and 20 minutes later spastic activity became general.
	Monkeys	Ataxia; poor hand to mouth coordination; one monkey developed convulsions followed by unconsciousness within the first week of exposure.

established that the brain was significantly affected in both groups of rats with vacuolization of protoplasm being the predominant change noted.

Belova and Yevtushenko (1967) performed visual pathologic examination of the rabbits exposed in the same study. In the initial weeks of the experiment, slight hyperemia of the conjunctiva and the appearance of a small amount of discharge from the eyes were observed. In animals of both groups (20 and 120 ppm) the optic disc was pale or grayish and frequently had diffused edges. Edema of the optic disc was noted in rabbits exposed to the higher level. Blood vessels of the eye were of uneven caliber, arterial vessels were primarily constricted, and small hemorrhages were noted in the retina of some animals. Histologic examination of the retina and optic nerve indicated morphologic changes, as well as increased vascularization, plasmorrhagia and hemorrhaging. No information on the optic system of the rats exposed at the same dose was given.

In the 90-day inhalation study of chloromethane sponsored by CIIT (see Section IV), rats exposed to 375, 750, or 1500 ppm exhibited no gross pathologic alterations of the eye. However, mice exposed to the 375 and 750 ppm dose had a high incidence of eye lesions that began as a mucopurulent conjunctivitis and progressed until some animals' eyes were totally destroyed (Battelle 1979).

2. Conclusions

The following conclusions on the neurotoxicity of chloromethane can be made:

(1) adult dogs and mice appear to be the species most sensitive to the chronic neurologic motor effects of chloromethane; and

(2) neurobehavioral symptoms seen acutely in monkeys and dogs are similar to those expressed in acute human toxicity.

Several investigators have detailed the permanent neurobehavioral effects of long-term exposure to chloromethane, Klimkova-Deutschova (1957) and Langauer-Lewowicka et al. (1974). In representative studies, groups of workers exposed to chloromethane exhibited chronic neurologic or behavioral changes from apparent long-term, low-level exposure; there were no stated high-level acute exposures. In a slightly different type of study, Repko et al. (1977) found significant decrements in complex math tasks, increases in resting tremor, and increases in the latency to visual stimuli in a group of occupationally-exposed workers. The EPA feels that while these studies suggest that long-term exposure to chloromethane may pose an unreasonable risk, they are inadequate to determine the extent of that risk.

Many problems have been encountered in evaluating animal studies. In several species of animals it was concluded that 300 ppm had "no apparent effect in 64 weeks of exposure" on any species tested, but that the acute effects of chloromethane in dogs and monkeys had much in common with neurologic symptoms described for humans acutely exposed (Smith and von Oettingen 1947a,b). More recent animal studies of chronic exposure have produced suggestive evidence of functional and pathologic effects after a shorter duration of exposure at lower concentrations (Yevtushenko 1966), although not enough information is presented in the papers to enable the EPA to adequately assess chloromethane's neurotoxicity.

3. Testing Under Consideration

While the Agency is not prepared at this time to propose standards for the conduct of neurobehavioral testing, set forth below are current views on the proposed testing, and related issues relevant to the development of these standards. Comments are solicited from all sectors on the appropriateness and conduct of the suggested testing.

The EPA is considering proposing animal studies to determine toxicity levels for neurobehavioral effects of chronic exposure. Among the variables to be determined are choice of species,

length of test, days per week exposed, type of exposure and type of testing. The EPA is asking for public comment on these issues.

One neurobehavioral area of concern has been identified for testing, namely, changes in function and morphology of the nervous system due to chronic exposure. Changes in complex cognitive functions and visual function as measured by behavioral tasks may be the most sensitive human indicators of exposure to chloromethane (Putz et al. 1979, Repko et al. 1977, Stewart et al. 1977). The report on exposed workers by Klimkova-Deutschova (1957) and the 13-year follow-up study of exposed fishermen by Gudmundsson (1977) suggest that chloromethane intoxication may produce signs of damage of the cranial nerves, other ocular involvement, pyramidal and extrapyramidal neurologic signs, a reduced tolerance to alcohol, fatigue, and depression.

The choice of species for animal testing will involve several considerations. First, Smith and von Oettingen (1947a) have suggested that effects in dogs and monkeys most resemble human intoxication. The inappropriateness of rats as a test species is suggested by the same authors' failure to observe any overt effects in rats but not in other mammalian species exposed to 500 ppm. On the other hand, Yevtushenko (1966) reported behavioral effects from both acute and chronic exposure at low levels in rats; the apparent discrepancy may be due to their use of quantified behavioral testing as compared to the presumably less objective observational techniques of Smith and von Oettingen (1947b). However, the reports of neither study are adequate to determine if this is, in fact, the case.

The Agency is also considering the appropriateness and best means of defining adequate post-exposure testing to assess the severity and persistence of any observed effects. If exposure in the chronic study is noncontinuous, post-exposure observation could be performed prior to the beginning of daily or weekly exposure.

In addition, the EPA is considering whether testing for abuse potential, interaction with ethanol and/or a mixed schedule of exposures (long-term low-level plus acute high-level) would be appropriate additions to the requirements. Details are presented in the Preamble.

C. Mutagenicity

1. Data Evaluation

a. Gene Mutation

A review of the data available shows that chloromethane is a direct-acting mutagen. This means that chloromethane does not have to be metabolized by mammalian enzymes to an active form. In bacterial systems capable of detecting gene mutations, chloromethane produces a strong, positive, reproducible dose-response curve of chemically induced mutations in Salmonella typhimurium strains TA 1535 and TA 100. These strains normally cannot synthesize the amino acid histidine and this must be added to the nutrient medium to support their growth. When the proper mutation occurs in the specific portion of deoxyribonucleic acid (DNA) of these organisms that regulates this effect, they are able to synthesize histidine and are then capable of growth in histidine-free medium. The bacterial strains which demonstrate chloromethane mutagenicity are mutated by agents which cause changes in a specific guanine-cytosine base pair, and possibly others in the DNA molecule as well. Agents such as chloromethane that cause substitutions of specific nucleotides are called base pair mutagens. S. typhimurium TA 1535 and TA 100 are the same basic strain; TA 100 is TA 1535 with the addition of a resistance factor, pKM 101, which confers resistance to the antibiotic ampicillin and, at the same time, increases the sensitivity to mutagenic agents.

After exposure to chloromethane, both with and without metabolic activation, increased numbers of bacteria of strains TA 1535 and TA 100 were capable of growth in histidine-free medium. On a quantitative basis, increasing concentrations of chloromethane caused the mutation of greater numbers of

bacteria. For example, in a population of approximately 1 x 10^8 strain TA 100 bacteria, there will ordinarily be approximately 100 bacteria capable of growth in histidine-free medium. Exposure to 2.5 percent chloromethane in the atmosphere increased this number to approximately 400 in 1 x 10^8; exposure to 20 percent chloromethane increased the number to approximately 1,100 in a total population of 1 x 10^8 bacteria (Simmon 1977). Similar results were reported by Andrews et al. (1976), and Haskell Laboratory (E.I. du Pont 1977). In this test system, therefore, chloromethane is a base pair mutagen which causes an alteration in at least one guanine-cytosine base pair of the DNA molecule.

In addition, Haskell Laboratory (E.I. du Pont 1977) tested chloromethane in two strains of S. typhimurium that detect frameshift mutagens (i.e., a mutagen which causes the addition or loss of nucleotide pairs), TA 98 and TA 1537, and reported it to be inactive. It is not uncommon, however, for a chemical which is a positive base pair mutagen to be inactive in a frameshift strain and vice versa. This is one reason that a good Ames test will include strains of both types of S. typhimurium. The EPA believes that positive results in only one strain are adequate to determine that a chemical may pose a risk of human mutagenicity and should be tested further. Given the universality of the structure of DNA, it is reasonable to assume that chloromethane may also cause base pair alterations in the DNA of higher organisms, including humans.

The Diamond Shamrock Corporation (1978a) has submitted a series of test results in which chloromethane is reported to be non-mutagenic for S. typhimurium strains TA 1535 and TA 100 and Escherichia coli ATCC 23221 and ATCC 23233 and inactive in a host-mediated assay in mice with strain TA 100 as the tester strain. However, the significance of these negative test results is questionable because of the experimental techniques reported. Chloromethane is a gas under conditions of normal temperature and pressure. To adequately test such substances in bacterial mutation systems requires special test methods and procedures

that were not mentioned in the reported study. The test as described in the Diamond Shamrock submission is a spot test. In a spot test, bacteria are incorporated into top agar and poured over a base plate of minimal medium. The test agent is then placed on the plate (either in crystalline form or on a liquid saturated filter paper disc) and allowed to diffuse into the medium. The formation of a ring or concentrated zone of mutant colonies in the vicinity of the test sample is generally considered to be a positive result. The report submitted by Diamond Shamrock states that 1 to 5 ug of test chemical (chloromethane was one of a series tested) were added to the plate with a spatula. The results of this assay are open to question because the spot test, as described, is inappropriate for testing a gas. In addition, the EPA feels that the evidence of a single negative test result conducted under less than optimal conditions is outweighed by the positive results obtained in three independent studies. The EPA, therefore, considers chloromethane to be mutagenic for S. typhimurium strains TA 1535 and TA 100.

Chloromethane was also reported to be inactive in a host-mediated assay in which S. typhimurium strain TA 100 was used as an indicator organism (Diamond Shamrock 1978a). The host-mediated assay employs an intact mammalian host as the activation system for a microbial mutagen. The test chemical is administered to animals over a period of time which may range from several hours to several days. At the end of the treatment period, the indicator organism (bacteria, yeast or some mammalian cells capable of growth in culture) is administered to the host animal and allowed to incubate, presumably in the presence of the test agent and/or its metabolites, over a period of several hours. At the end of the incubation period, the indicator organisms are removed and plated on a selective medium to determine mutation. The study submitted by Diamond Shamrock has severe problems. The test chemical was administered orally, dissolved or suspended in 10 percent ethanol or peanut oil, without specifying which was used for chloromethane and without

specifying how gaseous chloromethane was added to the solvent. Further, concentrations are given in mg/kg but with no indication of how this was determined. No positive control data were presented. In general, the test data are inadequate and not subject to critical review and evaluation. In addition, the variables inherent in this system, e.g., concentration of test agent in the animal, animal strain insensitivity, less than optimal amounts of test substance administered, failure of the test chemical or its active metabolites to reach the bacteria in effective amounts, or administration of either test agent or bacteria by the least effective route, may have resulted in false-negative or seemingly incongruous results with chloromethane in this assay. For these reasons, the EPA considers the aforementioned host-mediated assay test results to be of questionable value in assessing the mutagenic potential of chloromethane.

The EPA believes that in any instance where contradictory data is received on lower tier mutagenicity tests, even if all tests are well-conducted, further testing in a more sophisticated system is necessary to resolve the questions raised by the tests producing positive results.

b. Heritable Translocation

Chloromethane has also been reported to cause chromosome breaks in pollen grains of Tradescantia paludosa (Smith and Lotfy 1954). At the doses which gave the greatest response, chloromethane (9231 ppm) caused a higher percentage of chromatid breaks (240 breaks/5,932 chromosomes, or 4.04 percent) than did ethylene oxide at 7692 ppm (24 breaks/2,150 chromosomes, or 1.12 percent). At equivalent ppm (10,769) chloromethane was also more potent than ethylene oxide in causing chromatid breaks (3.09 percent vs. 0.65 percent). Chloromethane produced only chromatid breaks, however, while ethylene oxide also induced erosions and contractions, leading to a higher level of total chromosomal abnormalities than chloromethane at optimal levels (5.21 percent vs. 4.04 percent). There were six breaks per 6,590 chromosomes,

or 0.09 percent, in untreated control pollen grains. Ethylene oxide is one of the best-studied mutagens known and has demonstrated mutagenicity in almost every system in which it has been tested (USEPA 1978a).

Diamond Shamrock (1978b) also submitted the results of a rat dominant lethal study in which chloromethane proved to be inactive. A dominant lethal mutation is a change in the germ cell, either egg or sperm, which is lethal to zygotes produced by the mutated germ cell. In mammals, dominant lethal mutations will reduce litter size. This reduction in litter size can be due to the failure of the fertilized egg to implant or to develop after implantation has taken place. Brewen et al. (1975) have shown that dominant lethality results from chromosome breakage, and that the incidence of broken chromosomes at metaphase of the first cleavage of the fertilized egg corresponds to the incidence of dominant lethal eggs. From the tenth day of pregnancy onward in rats and mice, uterine contents can be recognized and classified into living embryos and early and late fetal deaths. Dominant lethal tests can be performed by exposing either male or female animals to the test substance and mating them with untreated members of the opposite sex. The test is most commonly performed by treating male animals and mating them to untreated females.

Diamond Shamrock's results are suspect for several reasons. First, as described by Diamond Shamrock (1978b), chloromethane was administered by oral intubation as a saturated solution in dichloromethane. Given the gaseous nature of chloromethane, exposure by inhalation is considered to be more appropriate and would have eliminated the need to use a solvent such as dichloromethane which is itself a biologically active material (see Sections III.E., and III.F.). In any case, a dichloromethane control should have been included in the study and this was not reported.

The assay is also difficult to evaluate because of apparent inconsistencies in the data and because of the manner in which

the data are presented (Diamond Shamrock 1978b). For instance, survival rates of the animals used for the positive control are shown in a table that presents survival data only and are presented later in a table which shows fertility data. The data in the two tables do not agree. The narrative text of the report and the survival data table imply that separate groups of animals were used as negative controls in the acute and subacute parts of the study, whereas the tables which present fertility data imply that the same animals served as negative controls for both parts of the study.

Another problem is that data necessary to properly evaluate such aspects of the study as corpora lutea counts and preimplantation loss, are not presented. Further, a table listing average implants fails to specify whether it is referring to total implants (live plus dead embryos), or living embryos only. In all, the data as presented are difficult to interpret, and do not lend themselves to statistical evaluation and critical review. As a result, the validity of the dominant lethal study as presented is open to question.

2. Current and Planned Testing

The EPA is planning on performing a Drosophila sex-linked recessive lethal test, a mammalian cell culture gene mutation test if the Drosophila test is negative and a dominant lethal test in rats.

3. Conclusions

There is evidence from bacteria and higher plants that chloromethane is capable of causing both gene mutations and chromosomal aberrations. In bacteria, chloromethane is a direct-acting mutagen capable of inducing base pair substitutions in the DNA of S. typhimurium strains TA 1535 and TA 100 (Andrews et al. 1976, E.I. du Pont 1978, Simmon 1977). In Tradescantia pollen grains, chloromethane is more effective than ethylene oxide in inducing chromatid breakage (Smith and Lotfy 1954). Although this information indicates that exposure to chloromethane may present an unreasonable risk of mutation to humans, it is insuf-

ficient by itself to assess chloromethane's risk as a potential human mutagen.

4. Testing Under Consideration

In recent years, mutagenicity experts have discussed, and provided guidance on, hazard estimation procedures for determining if a chemical is a potential human mutagen. The EPA's decisions concerning mutagenicity testing for chloromethane is based upon the guidance discussed below.

Between 1975 and 1979 four major reports on the hazards of environmental mutagens were issued (Drake 1975, Flamm 1977 McElheny and Abrahamson 1979, NAS 1977); in 1978 the Office of Pesticide Programs proposed Guidelines for Registering Pesticides in the U.S. (USEPA 1978b).

The reports agree that to perform a mutagenicity hazard estimation for humans, scientists must first demonstrate that a substance and/or its metabolite(s) does or does not cause heritable gene or chromosomal mutations (the two classes of mutagenic damage which have been shown to be responsible for a portion of human genetic disease) and whether the active form can reach the significant target molecules in mammalian germinal tissue.

A discussion of the principles and practices of mutagenicity testing in terms easily understood by persons unfamiliar with mutagenicity is presented in the EPA's booklet "Short-Term Tests for Carcinogens, Mutagens and other Genetoxic Agents" (Trontell and Connery 1979).

The rationale for utilizing mutagenicity data which are not derived from humans (all present data) has been previously detailed (OPP 1978) and is based on an extensive body of knowledge in the field of genetics. The following points are essential to such a rationale and are generally accepted by experts in the field of mutagenesis (see e.g., Drake 1975, Flamm 1977, McElheny and Abrahamsom 1979, NAS 1977). They are:

(1) All organisms (except for a few viruses) have DNA as the genetic material which is basic for survival and reproduction;

(2) The DNA code is the same in all organisms;

(3) The cellular machinery for decoding the information stored in the DNA code is similar among all organisms;

(4) Eukaryotic organisms contain nuclei in their cells, and their DNA is associated with protein to form complex bodies called chromosomes. Prokaryotic organisms lack nuclei, and their chromosome structure differs from that of eukaryotic organisms;

(5) Unless there is a mutational event, the information in DNA is faithfully replicated in each cell generation in unicellular organisms and in somatic and germ cells of multicellular organisms;

(6) DNA can be altered by chemicals. If this damage is repaired properly there is no mutation. If it is repaired with error or not repaired prior to replication of DNA, mutation can result. A single lesion in DNA may lead to a mutation;

(7) Point mutations usually involve changes in the bases of the DNA chain: the replacement of one purine or pyrimidine DNA unit by another is called base pair substitution: insertion or deletion of a base pair into the DNA chain is called a frameshift mutation;

(8) Breaks in DNA may lead to structural chromosomal aberrations;

(9) Disturbances in the distribution of individual chromosomes or chromosome sets can occur during cell division and result in numerical chromosomal aberrations; and

(10) Mutations are generally considered to be deleterious in reference to the normal environment for an organism and to result in decreased survival and reproduction.

Although not all mutations are deleterious (e.g., the Ames test measures a mutation which is advantageous to the organism), it is impossible to tell if any alteration in the genome would be good, bad, or of no importance.

Given the ubiquitous nature of DNA as the genetic material, the universality of the genetic code, and the similarity in response of genes and chromosomes of various lifeforms, a rationale for using the results from different test systems develops. Humans, as well as bacteria, fungi, and higher eukaryotes suffer DNA damage and gene mutations; humans, as well as other eukaryotes, show structural and numerical chromosomal aberrations. For these reasons, cells of any species may be used to detect genetic changes and to predict genetic change or damage in other species.

There are two single tests each of which measures one of the genetic endpoints (gene mutation or chromosomal aberration) and the ability of the mutagenically active form of a chemical to reach germinal tissue. These tests are the mouse specific locus test which detects gene mutations, and the heritable translocation test which detects chromosomal aberrations in mice as its genetic endpoint.

The EPA is requiring neither a mouse specific locus test nor a heritable translocation test at present. Although evidence in the lower orders suggests that there is a possible risk to man, the EPA believes that the most appropriate approach for this effect is to use a sequenced testing scheme. However, while the

tests for such a scheme are available, at this time the Agency is unable to propose triggers for the process, i.e., criteria for determining whether a given result is positive of negative. While such triggers are being defined, the EPA is planning to perform and evaluate a Drosophila sex-linked recessive lethal test, a mammalian cell culture test if the Drosophila test is negative, and a dominant lethal test. The EPA will require the higher sequenced testing if the results of these tests indicate the need. For more details see the Preamble.

D. Oncogenicity

1. Data Evaluation

a. Mutagenic Activity

As described earlier, chloromethane has been reported to possess mutagenic activity in bacterial systems that detect gene mutations and to cause chromosomal aberrations in higher plants (see Section III.C.1. for detailed discussion and evaluation of each of these studies). In assays employing S. typhimurium test strains TA 1535 and TA 100, the chemical induced a strong, positive dose-dependent mutagenic response, both with and without metabolic activation (Andrews et al. 1976, E.I. du Pont 1978, Simmon 1977). These tester strains detect base pair mutagens. In Tradescantia paludosa pollen tubes, chloromethane increased the chromatid breakage rate about forty-fold (Smith and Lotfy 1954). Considering chloromethane's activity in S. typhimurium strains TA 100 and TA 1535 and in Tradescantia paludosa pollen tubes, the EPA considers chloromethane to be a direct acting mutagen (i.e., it does not have to be metabolized to be active).

The concept that neoplasms arise from mutations in somatic cells was originally postulated by Boveri in 1914 to account for both the unlimited variety of tumor types, and the fact that daughter cells maintain their neoplastic properties upon cell division (Chu et al. 1977, Trosko and Chang 1978). Oncogens and mutagens have two properties in common: 1) the ability to induce new properties in cells that can be transmitted to their daughter cells; and 2) the ability to convert normal cells into

irreversibly changed cells (Suss et al. 1973). Although the mutation theory of oncogenesis has not been confirmed, the validity of the theory has recently gained more attention because of three important findings. First, in the 1960's, the Millers at the University of Wisconsin discovered that the majority of oncogens need to be metabolized in order to be active (Miller 1978, Miller 1979, Miller and Miller 1974); second, in vitro metabolic activation systems which could be incorporated into mutagenicity assay systems were developed (Malling and Chu 1974); and third, comparison of the ultimate reactive metabolites of structurally diverse oncogens and mutagens revealed that the common denominator of these substances is their electrophilicity, (i.e., they are compounds whose atoms have an electron deficiency that enables them to react with electron-rich sites in cellular nucleic acids and proteins) (Bartsch 1976, Miller 1979). These three findings have now been verified by a host of experimental data which show that many oncogens can induce different types of mutations including gene mutations (both base pair substitution and frameshift alterations), chromosomal aberrations, and non-disjunctions. The oncogenic potential of a chemical has also been correlated with its ability to interact with and modify DNA (Rosenkranz and Poirier 1979).

A wide variety of assay systems have been developed to detect effects on genetic material, including gene mutations and chromosomal aberrations. The particular value of one test, the Ames test, to the EPA's work is that it can be used as a indicator of oncogenic potential. A good correlation between mutagenic activity and oncogenic activity has been demonstrated (Bartsch 1976, Brusick 1979). Eighty to ninety percent of the known oncogens tested in this system have been positive. The number of false positives is also low in this system, ranging from 10 to 15 percent.

b. Alkylating Capabilities

Chloromethane is an alkylating agent. Alkylating agents belong to a larger class of reactive compounds called

electrophiles (electron-seekers). Representative animal tests show that some members of virtually all classes of alkylating agents are oncogenic (Lawley 1976). The basis for their biologic effect is the chemical modification of cellular DNA by these agents (Singer 1975). Oncogenesis by alkylating agents has been reviewed (Lawley 1976) as well as their effects on nucleic acids and the relationship of those effects to oncogenesis and mutagenesis (Pegg 1977, Singer 1975).

With chloromethane the methyl group is transferred to a nucleophilic (electron-donating) atom of another molecule with simultaneous elimination of chloride ion, to form a new, stable covalent carbon-heteroatom bond; that is, the nucleophilic reactant is alkylated, or in this case methylated. Chloromethane is a commercial alkylating agent, e.g., used to produce tetramethyllead (von Oettingen 1964). The chemical also has alkylating activity in both human (in vitro) and rat (in vivo) tissues (Redford-Ellis and Gowenlock 1971a, Reynolds and Yee 1967), forming primarily S-methylglutathione and S-methylcysteine.

A closely related compound, iodomethane, with an iodine (a larger halogen) instead of a chlorine, is also an alkylating agent. There has been some research on the oncogenic potential of iodomethane. Iodomethane has been shown to induce lung adenomas in strain A mice following intraperitoneal injection (Poirier et al. 1975) and to cause local sarcomas with lung metastases in rats following subcutaneous injections (Druckrey et al. 1970). The development of lung adenomas in strain A mice is considered to be a sensitive indicator of the oncogenic activity of alkylating agents such as iodomethane (Poirier et al. 1975, Weisburger 1978). In the case of iodomethane, 0.31 mmole/kg (44 mg/kg) given over a 24-week period (3 times per week) induced a significant increase in the average number of lung adenomas per mouse. In fact, iodomethane on a mmole basis was more active than urethane, which is the usual positive control used in this assay system. In the Druckrey et al. studies (1970), all 6 rats receiving 20 mg/kg of iodomethane once a week for a year

developed sarcomas at the site of injection. Of 12 rats receiving 10 mg/kg once a week for a year, 11 developed sarcomas at the site of injection. Another important finding was that in most cases the tumours had metastasized to the lungs. The latter information indicates the malignant nature of the induced tumors. Although neither of these studies provides sufficient information on iodomethane oncogenicity to do an adequate hazard assessment, at the least they do indicate that it has oncogenic potential. While both chloromethane and iodomethane are alkylators, knowledge of their relative alkylating abilities indicates that iodomethane would be the more potent.

c. Structural Relationships

Known chemical oncogens comprise a structurally diverse group of synthetic and naturally occurring organic and inorganic chemicals (Miller and Miller 1974, Miller 1979). Although knowledge of the chemical structures of known oncogens currently provides no way of definitively assessing molecular structures of unknown oncogenicity (Fishbein 1977), certain structural criteria for suspecting chemicals of oncogenic activity have been determined (Arcos 1978). Meeting these criteria are halogenated hydrocarbons and alkylating agents. Chloromethane falls into both categories. Its alkylating properties have been discussed in the preceding subsection.

d. Other

In addition, CIIT has reported the development of 37 nasal squamous cell carcinomas in rats exposed to formaldehyde (a metabolite of chloromethane) at 15 ppm (CIIT 1979). The study is not complete, but the discovery of such numbers of rare tumours in this species is important. Exposure to formaldehyde was by inhalation, and the carcinomas were found in the nose, so that the irritant effect and localized high levels may play a part in the oncogenicity. Also, the production of formaldehyde as a metabolite of chloromethane might lead to different results, because concentrations would be expected to be low. While

demonstration that a metabolite of a chemical is an oncogen is not sufficient by itself to establish that the initial compound will cause tumors, under some circumstances such a finding may support a request for further testing.

2. Conclusions

After reviewing the evidence available on the oncogenic potential of chloromethanes, the EPA finds that chloromethane may present an unreasonable risk from oncogenicity. While there is no direct evidence in humans or in animals that chloromethane is an oncogen, various indirect evidence indicates that it has oncogenic potential. The indirect evidence is summarized as follows:

a. chloromethane is a mutagen: (1) inducing gene mutations in bacteria and (2) causing chromosomal aberrations in plants;

b. chloromethane is a direct alkylating agent known to alkylate human and animal tissues;

c. halogenated hydrocarbons such as chloromethane are among the classes of chemical compounds known to have oncogenic activity; and

d. chloromethane is metabolized to formaldehyde, a known animal oncogen.

3. Current and Planned Testing

CIIT is at present running a two-year study of the effects of chloromethane on rats and mice, which involves exposure of the animals for twenty-four months, 6 days a week, 6 hours a day.

Because of the deficiencies discussed earlier under III.A.2, such as the premature decease of most of the male mouse population, the EPA believes that the ongoing test is insufficient and that there is a need to conduct a new, long-term bioassay.

4. Proposed Testing

The EPA proposes to require that a 2-year oncogenicity study be undertaken to determine the oncogenicity potential of chloromethane in animals. Test standards have been proposed by the EPA (USEPA 1979b). The EPA is, however, proposing that because of the relative insensitivity of the rat to the toxic effects of chloromethane as discussed in Sections III.A. and III.B, that the species used in the oncogenicity study be mice and hamsters. Although systemic toxicity and oncogenicity are different endpoints, and the factors that affect one such endpoint in any species may not affect the other, the converse may also be true. Differences in parameters such as absorption or distribution may account for species variability in systemic toxic effects and these same parameters may also affect the ability of the compound to reach a potential target organ. It is the EPA's belief that testing of the most responsive species to any toxic effect will allow the Agency to better evaluate possible risk. Because there is no information to indicate why the rat is less affected with regards to systemic toxicity, the Syrian hamster is being proposed as a replacement. The EPA welcomes comment from the public both as to theoretical basis for this proposal, and the choice of a substitute test species.

E. Teratogenicity

1. Data Evaluation

a. Structural Teratogenicity

Only one report associating the birth of a severely deformed child with maternal exposure to chloromethane and ammonia vapors is available (Kucera 1968), and it does not give details as to dose, time, or length of exposure. To date no animal studies to evaluate the effects of chloromethane on the fetus have been published. However, Smith and von Oettingen (1947a) reported that "a rabbit conceived and born during exposure to 500 ppm grew at a normal rate during 33 weeks of exposure", but developed slight neuromuscular symptoms like those

seen in adults. Because exposures continued after birth, and only one rabbit was so exposed, no conclusion can be drawn from this study.

A lipid-soluble, small molecular weight gas such as chloromethane would be expected to cross the placenta readily (Villee 1971, Nishimura and Tanimura 1976). Although no direct evidence of chloromethane induced fetal toxicity has been found, Hartman et al. (1955) tell of a seven-month pregnant woman severely poisoned by chloromethane. When the unconscious woman was found, the fetus had been aborted and was still attached to the undelivered placenta.

b. Behavioral Teratogenicity

Additional concern for the teratogenic potential of chloromethane is based on its documented neurotoxicity. The central nervous system appears to be especially susceptible to toxic insult during its development (Buelke-Sam and Kimmel 1979). The period during which the CNS develops is an extended one and vulnerability to toxic insult continues into the post-natal period. The possibility of fetal exposure to a neurotoxicant such as chloromethane warrants its evaluation as a teratogen. Evidence has been presented that suggests that both structural and behavioral deficits in adult and developing systems are associated with exposure to other nonspecific CNS depressant chemicals (van Stee 1976). Few purely behavioral teratogens are known at this time, but psychotropic drugs which have little or no structural teratogenic potential have been identified as behavioral teratogens (Vorhees et al. 1979a). Chloromethane, a neuroactive drug, therefore, may have the potential, when introduced *in utero*, for causing postnatal neurobehavioral problems, even if no classical terata are produced. Recent experiments by Bornschein et al. (1980) demonstrate behavioral defects in rats exposed *in utero* to dichloromethane at a dose which caused no morphologic defects (Hardin and Manson 1980).

2. Current and Planned Testing

Although CIIT has not yet initiated its teratology testing, they have proposed a protocol for teratologic evaluation of chloromethane (Tyl 1979). Using this protocol, CIIT intends to collect data on anatomical abnormalities, neurofunctional deficits, and acquisition of developmental landmarks in rats exposed to chloromethane *in utero*.

The CIIT protocol differs significantly from that proposed by the EPA (USEPA 1979a) in several ways:

(1) It specifies the use of a single species, the rat, to evaluate teratogenic effects. The EPA has proposed teratology testing in a minimum of two mammalian species. A study in one with negative results would be considered inadequate, although findings of malformations in a single species would be highly suggestive of teratogenesis.

(2) The dosage selection procedure proposed by CIIT bases the two lower doses on multiples of the TLV, which may not conform to suggested criteria for dosage levels as published in the proposed Test Standards (USEPA 1979a). The proposed EPA standard for the teratogenicity study includes a high dose which should produce some maternal toxicity, an intermediate dose which ideally should produce some fetal toxicity, and a no-effect dose.

(3) Although the battery of tests for the evaluation of neurofunctional deficits and the acquisition of developmental landmarks proposed by Tyl (1979) may not be completely appropriate, standards for the testing of behavioral alterations have not yet been proposed by the EPA. The Agency will consider CIIT's proposed battery as the basis for such testing.

(4) Because the rat has demonstrated low sensitivity to the toxic effects of chloromethane (Smith and von Oettingen 1947a), other species perhaps should be considered for the teratogenicity testing.

3. Conclusions

On the basis of chloromethane's neurotoxicity in adults, accessibility to the fetus and in agreement with the concept that structural and functional evaluations are complementary approaches to CNS toxicity (Barlow and Sullivan 1975, Langman et al. 1975), the EPA concludes that chloromethane has a potential for teratogenicity in the human for both behavioral and structural malformations.

4. Testing Proposed and Under Consideration

a. Structural Teratogenicity

Standards for the development of data on morphologic teratogenic effects have been proposed (USEPA 1979a). These standards relate to the development of data on anatomic abnormalities.

Although CIIT is planning on performing a teratology study, the differences in protocol may yield results which would not completely satisfy the Agency's concern about teratogenic effects. For that reason the EPA is proposing a test rule for structural teratogenicity testing. However, if data are submitted to the EPA to demonstrate that the test, as performed, will be sufficient to evaluate chloromethane's teratogenic potential, this test rule will be reconsidered before final promulgation.

The EPA believes that its proposed teratogenicity test standards are appropriate for the testing of chloromethane for the induction of these effects, with one exception. The Agency is proposing that the rat not be used for teratogenicity testing, because of a demonstrated lack of sensitivity of this species to

the toxic effects of chloromethane. As stated previously, insensitivity to one toxic endpoint may not be reflected by a similar insensitivity when observing a different effect. This is particularly true when related to classical teratology. The production of severe malformations in the offspring of exposed mothers has had, at times, little correlation with the systemic toxicity of the compounds, as exemplified by the case of thalidomide. There are however, certain factors which may affect both endpoints (parameters such as absorption or metabolism), and until these are ruled out as the cause of the rat's insensitivity, there is the significant possibility that the insensitivity may carry over to structural malformations as well. In addition, the structural teratogenicity test measures such aspects as embryo- and fetotoxicity, stunting and delayed development, which may be a reflection of the compound's systemic toxicity, or its effects on the dam. In either of these instances, the more responsive a species is to the chemical to be tested, the better equipped the Agency will be to estimate potential hazards from exposure to the compound. The EPA requests comment on these issues.

b. Behavioral Teratogenicity

The EPA feels that an evaluation of neurologic/behavioral abnormalities and of the acquisition of developmental landmarks is necessary to assess the possible teratogenicity of chloromethane (see, e.g., Vorhees et al. 1979b). Since no standards for the development of this type of data have been proposed, this topic will be subject to public comment before a rule is proposed.

In addition to routine signs of physical development that may reflect toxicity (e.g., body weight), the proposed testing should include specific tests to assess in the offspring known effects of chloromethane in adults. Acquisition of a conditioned reflex was reported as a sensitive endpoint by Yevtushenko (1966). Neurologic impairment of motor function in humans and other mammals has been reported (see, e.g., Klimkova-Deutschova

1957, Smith and von Oettingen 1947b) and impairment of visual functions in humans (see, e.g., Langauer-Lewowicka et al. 1974). These three types of endpoints should be considered as well as thorough neuropathology.

F. Metabolism

1. Data Evaluation

a. Absorption

Although it is generally believed that the principal route of human exposure to chloromethane is by inhalation, most inhalation experiments in both man and animals are really whole-body exposure experiments and possible skin and GI absorption cannot be wholly ruled out (Bus 1979, Smith and von Oettingen 1947a, Stewart et al. 1977, Yevtushenko 1967). It has been demonstrated, moreover, that chloromethane can be absorbed through the skin (NIOSH 1977). In another experiment (Morgan et al. 1970) the human volunteers inhaled the radiolabeled chloromethane directly through a tube placed in the mouth (which allows the possibility of GI or mucous membrane absorption, but does eliminate that through the skin) and showed that absorption through the airways probably does occur.

b. Distribution

Several different experimenters have followed blood and tissue levels of chloromethane over time. The experiments are of two types: 1) disappearance of chloromethane from the tissue is followed after a single brief exposure, either by injection or inhalation; and 2) those in which the subject has been exposed for a considerable period of time (i.e., the condition is more or less stabilized) and the levels of the chemical are followed after cessation of exposure.

Sperling et al. (1950) injected chloromethane into dogs intravenously (i.v.) and measured blood and tissue chloromethane at various times. At the first measurement just after the injection was completed, the percentage of chloromethane present in the blood varied between 4.5 and 13.1 percent (of 1680 mg

injected); at 30 minutes, the values were 1.5 to 2.7 percent; and at 60 minutes they ranged from 0.6 to 1.3 percent. However, between eight and thirty minutes were required to inject the total amount of chloromethane (as a gas), thus allowing time for some redistribution to tissues and for biotransformation. This group did another series of experiments in which they measured blood and tissue levels in one group of animals immediately following injection of various amounts of chloromethane (173-206 mg/kg), and another group (154-228 mg/kg) after one hour. The blood chloromethane concentration initially ranged between 0.119 to 0.135 mg/cc, while at one hour, the range was 0.035 to 0.041 mg/cc. Neither of the groups showed a dose-blood level relationship, however. Various other tissues were measured for chloromethane content during the same experiment, with similar results occurring. Levels at 60 minutes were on the average lower than those at the beginning, although there was considerable variation among dogs.

Soucek (1961) used subcutaneous (s.c.) injection in rats to measure the disappearance of chloromethane from the blood. At two minutes following a single 1200 ug injection of chloromethane in H_2O, 1.4 percent of the dose appeared in the blood, at 10 minutes 0.7 percent, while at 25 minutes, chloromethane concentrations were below the level of detection. However, it is difficult to compare the two experiments, as Soucek could not or did not measure the rate of chloromethane's entrance into the blood, and measurements made after s.c. injection are the result of a two-way flow, both into and out of the blood. Although Soucek was unable to measure chloromethane in the blood beyond 10 minutes, he was still able to detect unaltered chemical in the expired air at 120 minutes, as were Sperling et al. (1950).

CIIT's study (Bus 1979) is of the second type, but with an additional change. Instead of measuring chloromethane, CIIT administered $^{14}CH_3Cl$ and measured radioactivity, which enabled the investigators to pick up metabolites and bound compound as well as free compound dissolved in the plasma. Blood ^{14}C-levels

were measured at intervals following a 6-hour exposure to 1500 ppm in rats. At time zero (immediately after the 6-hour exposure), the ^{14}C-content of the blood was 0.93±0.02 umole of CH_3Cl equivalents/ml, after which the level steadily dropped until at 24 hours (30 hours from start of experiment) the value was 0.17±0.02, umole CH_3Cl equivalents/ml. Levels in all other tissues measured (liver, fat, kidney, spleen, lung, heart and brain) acted in a similar manner. However, some tissues lost radiolabel much more quickly than others. At 24 hours the amount of ^{14}C in fat was 12.1 percent of the initial value, while the heart still carried 38.9 percent of its initial load. At time zero, liver was highest with 2.63 umole CH_3Cl equivalents/g wet weight, while brain had the lowest concentration, 0.55 umole, but at 24 hours levels in all the tissues were closer to each other, from liver with 0.45 to brain with 0.12 umole CH_3Cl equivalents/g wet weight. There is apparently little or no redistribution to other tissues, nor are the organs which appear to be most affected (i.e., brain, liver, kidney) those which retain the greatest amounts of radioactivity.

c. Excretion

Some portion of the gas is excreted unchanged, not only through the lungs in man (Morgan et al. 1970, Stewart et al. 1977), dogs (Sperling et al. 1950), and rats (Soucek 1961), but in the urine and bile following i.v. injection in the dog (Sperling et al. 1950). CIIT (Bus 1979) also claimed that a portion of the administered chemical was found in the expired air (radiolabel trapped in a charcoal filter but not chemically identified). Under the conditions of the study (6-hour inhalation of different dose levels by rats and mice, 48 hour observation period) the amount excreted unchanged was fairly small and did not appear to be strictly dose-dependent. In rats, at 100 ppm, 2.4 percent of the retained material was found in the expired air, at 375 ppm, 1.8 percent, and at 1500 ppm, 6.3 percent; in mice, at 1500 ppm, 4.4 percent was exhaled (Bus 1979).

Sperling et al. (1950), following injections of various amounts of chloromethane into dogs, observed that about 5 percent of the total injected was found unchanged in the expired air within the first hour. However, Morgan et al. (1970) found that one hour after inhalation of $CH_3{}^{38}Cl$ in man, 29 percent of the administered radioactivity was excreted through the lungs. The EPA believes that all the radioactivity measured in the expired air was chloromethane, rather than a metabolite, even though this was not verified chemically, as all the known or postulated biotransformation mechanisms produce chloride ion, a non-volatile product. The rather large difference between these two results may be due to the mode of administration, to the species, or to what was measured in the expired air: chloromethane in the first case (Sperling et al. 1950) and ^{38}Cl in the second (Morgan et al. 1970).

Morgan et al. (1970) compared the pulmonary excretion of $CH_3{}^{38}Cl$ with that of the higher chlorinated methanes, and concluded that chloromethane acted in a different manner. When excretion rate versus time was plotted (retention curve), the di-, tri- and tetrachlorinated methanes had parallel slopes, while monochloromethane's rate of excretion dropped more rapidly with time. This may be due to a number of reasons: 1) the compound is more reactive; 2) a greater percentage is excreted by alternate routes; 3) it is more fat-soluble. The authors felt that chloromethane behaved like iodomethane, which reacts rapidly with sulfhydryl groups in the erythrocyte in an enzyme-catalyzed methylation process.

Stewart et al. (1977) discovered two populations among their human subjects. Four of their subjects, as well as two from a previous study, had considerably elevated post-exposure breath and blood chloromethane levels. The rest of the volunteers carried a two to six times lower body burden than these. Stewart and his coworkers postulated that the worker who carries a lower body burden than the majority may be at greater risk from chloromethane exposure. This would appear to indicate that a larger

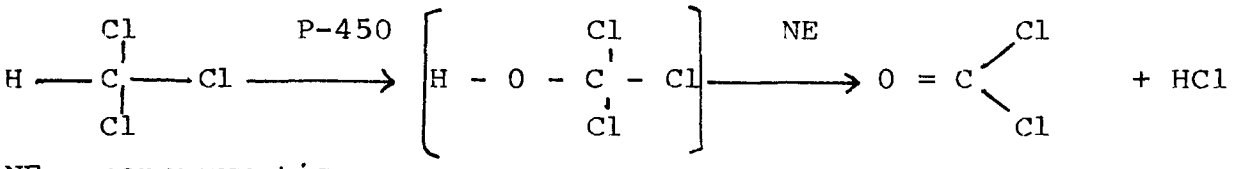
portion of the exposed population would be at greater risk. The data can also be interpreted to mean that those people with greater amounts of unaltered compound in their bloodstream and airspace might be metabolizing less of the material rather than absorbing or carrying more. And as the metabolized material is probably responsible for toxicity, the subjects excreting more compound unchanged would be at a lower risk rather than a higher one. If, on the other hand, chloromethane per se is the toxic compound, those persons with higher blood and breath levels may be more susceptible to overexposure. Of course, the possibility exists that neither of these theories is important, and the different populations are at equal risk.

d. Biotransformations

The earliest theories about chloromethane's biotransformation (Flury 1928) dealt with its probable conversion to formaldehyde through methanol. Formaldehyde has been found in the blood of rats (Yevtushenko 1967) and mice (Sujbert 1967) following inhalation of chloromethane, and in mice (Sujbert 1967) following intraperitoneal (i.p.) injection. Sujbert (1967) also was able to detect methanol in the bloodstream of mice following inhalation or i.p. injection as did Hayhurst and Greenburg (1929) who detected methanol, formaldehyde and formates in the organs of victims of chloromethane poisoning. Smith (1947), on the contrary, was unable to find any methanol in the blood of dogs that had been exposed to chloromethane by inhalation for 23 or 25 days. Other researchers have tested for formate in the urine or tissues of subjects exposed to chloromethane, with variable results. Baker (1927), Kegel et al. (1929) and Hayhurst and Greenburg (1929) found formates in human tissues and urine following accidental exposure to the compound, whereas Hansen et al. (1953) were unable to demonstrate increased formate in their human subjects correlating with levels of chloromethane in the ambient air.

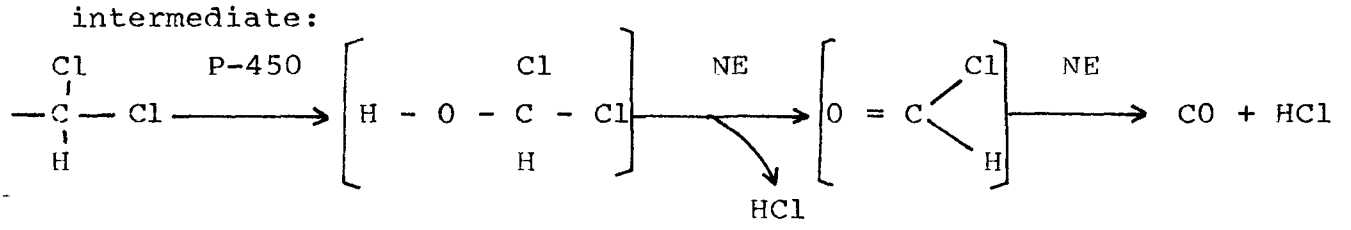
The creation of formaldehyde from chloromethane is probably analogous to that proposed for the biotransformation of

chloroform ($CHCl_3$) to phosgene, a reaction that has recently been confirmed experimentally (Pohl et al. 1977, 1979, Pohl and Krishna 1978).

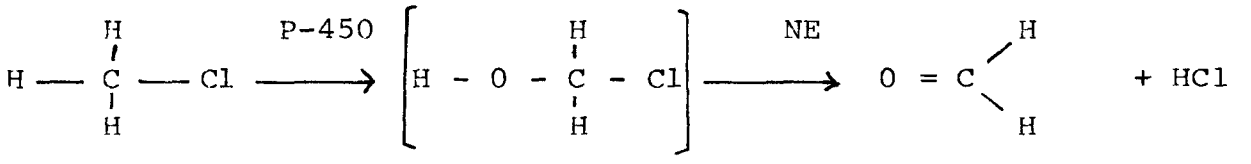


NE = nonenzymatic

It has been suggested that a cytochrome P-450 monooxygenase oxidizes $CHCl_3$ to unstable trichloromethanol, which spontaneously dehydrochlorinates to yield the reactive phosgene. Dichloromethane seems to follow a similar initial pathway (Kubic and Anders 1978) to eventually yield CO through a formyl chloride intermediate:



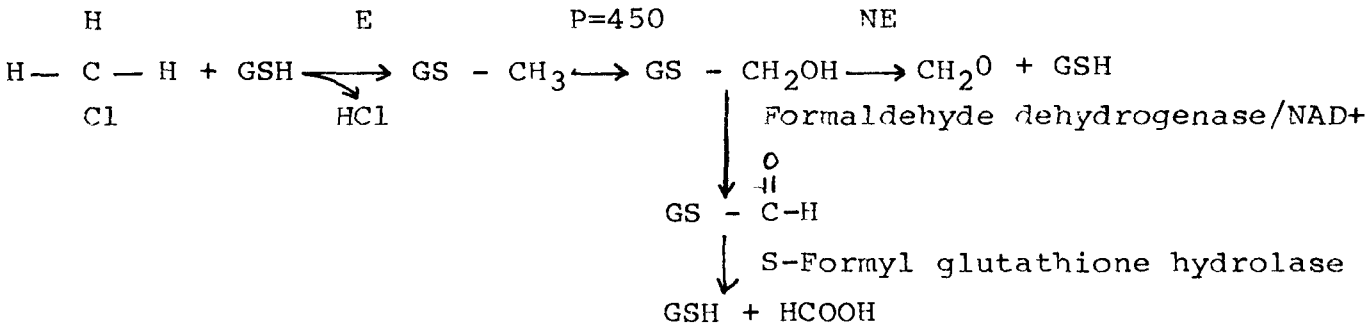
Formaldehyde production from chloromethane probably occurs as follows:



Additional reactions can occur after formaldehyde production: (1) aldehyde reduction, with formaldehyde going to methanol; (2) aldehyde dehydrogenation, with formic acid and/or formates as the ultimate product.

Ahmed and Anders (1978) have proposed an additional route for metabolism of dihalomethanes, which involves alkylation and dealkylation of glutathione (GSH). This pathway yields formaldehyde, formic acid and inorganic halide. As it is known that chloromethane binds very specifically to GSH in erythrocytes

(Redford-Ellis and Gowenlock 1971a), this alternative route may also be important for chloromethane.



E = enzymatic

CIIT (Bus 1979) measured radioactivity in the expired air for 48 hours following a 6-hour exposure to chloromethane in rats and mice. That percentage of radioactivity trapped by a charcoal filter they designated as chloromethane, while that trapped by ethanolamine in methoxyethanol was considered to be CO_2. No mention was made as to whether such possible alternative volatile metabolites as carbon monoxide, methanol, or formaldehyde would be trapped and measured by their methods.

CIIT (Bus 1979) found that in rats in the 48 hours following a 6-hour exposure to 1500 ppm $^{14}CH_3Cl$, more than 41 percent of the total recovered radioactivity was $^{14}CO_2$ from the expired air, while in mice given the same dose, less than 18 percent was excreted as $^{14}CO_2$. In mice, the largest percentage of recovered radioactivity (60 percent) was excreted in the urine, while the rat excreted only 40 percent of the retained radioactivity as urinary components. It is possible that a portion of the urinary radioactivity occurs as bicarbonate, for following acid hydrolysis of the mouse urine, a small portion (9 percent) of the urinary radioactivity was found in the headspace of the vial, presumably as $^{14}CO_2$.

e. Tissue Retention

In addition to measuring radioactivity in the various excreta, CIIT (Bus 1979) measured radioactivity retained in some organs and the carcass following exposure to $^{14}CH_3Cl$. In rats at the end of a 48 hour period following 6 hours of exposure to 100, 375 or 1500 ppm of the gas, there was no increase in the amount of associated radioactivity between the 375 and 1500 ppm groups (e.g., for liver at 100 ppm, tissue radioactivity equalled 52.3 umole of ^{14}C-chloromethane equivalents/g wet weight, while at 375 ppm, the radioactivity was 325.2, and at 1500 ppm, it was 265.2), which may indicate a saturation of available binding sites. Of the amount retained following a 6 hour exposure, 22.5 percent of the radioactivity was associated with the tissues at 100 ppm, 21.4 percent at 375 ppm and 17.3 percent at 1500 ppm. Although neither the form nor the type of binding in the tissues was specified by CIIT, the retention of such a high proportion of radioactivity after two days indicates a fairly strong binding capacity. At all dosages, retention was lowest, by a factor of three, in the brain, highest in the liver at 375 and 1500 ppm and highest in fat at 100 ppm. In mice following a similar exposure regimen at 1500 ppm, only 8.3 percent of the total recovered was associated with the tissues, and while the brain again had the lowest value, liver and kidney had the highest.

f. Binding

Morgan et al. (1970) postulated that chloromethane acts like iodomethane, reacting rapidly with sulfhydryl groups in an enzyme-catalyzed methylation process. Redford-Ellis and Gowenlock (1971a,b) studied the reaction of ^{14}C-chloromethane with human blood *in vitro*. In serum or plasma, about 65 percent of the radioactive uptake was associated with plasma protein but only about 2-3 percent covalently bound to the plasma protein (specifically albumin), producing primarily S-methylcysteine, although minor radioactive components of 1-methyl- and 3-methyl-histidine were also found. In erythrocytes, uptake was independent of dose over the range used (600-1000 mg/ml

erythrocyte), being a constant 357 mg/ml erythrocyte after 80 minutes, of which 58-130 mg was bound covalently to GSH. However, in studies on red cells, after uptake was complete, no radioactivity was lost by hemolysis or by washing, and no radioactivity could be detected bound to other components of the erythrocyte, so there appears to be some discrepancy between uptake and binding. Heating the blood before adding the chloromethane reduced binding by over 90 percent, indicating a probable enzyme-catalyzed reaction. Redford-Ellis and Gowenlock (1971b) continued their researches by studying chloromethane's binding to rat brain, liver and kidney homogenates in vitro, as these are the organs primarily associated with chloromethane toxicity. In all these tissues, the primary products are $^{14}CH_3$-S-Cys and $^{14}CH_3$-S-GSH, while in the kidney additional traces of radioactivity were found in methionine. The formation of these compounds in tissue homogenates also appears to be partially enzyme-dependent, as heating the tissues reduced the level of binding.

As part of the CIIT study, Dodd et al. (1979) looked at alterations in tissue sulfhydryl concentrations in rats after acute inhalation exposure to 1500 ppm chloromethane for 6 hours. They found that although changes in total tissue sulfhydryl groups were minimal at all times (0,1,2,4,8,18 hours) after exposure, non-protein sulfhydryl content was reduced in liver, kidney, lung and blood (most to least) indicating a decrease in free, reactive, -SH groups. At eighteen hours after exposure non-protein sulfhydryl content had returned to control values. However, earlier work by the same group (Bus 1979) reported that radioactivity was still present in these tissues 48 hours after exposure. It appears to the EPA that either: 1) significant amounts of CH_3Cl or a metabolite are reacting with non-sulfhydryl groups or 2) rearrangement is occurring.

2. Current and Planned Testing

CIIT has informed the EPA that they have not finished their total planned metabolism studies on chloromethane. It is

believed that these additional tests will substantially add to the corpus of knowledge of the compound.

3. Conclusions

The EPA is not proposing metabolism studies. Although information is incomplete, it is felt that the additional testing being done by CIIT is sufficient to aid the Agency in assessing chloromethane.

G. Epidemiology

In the case of chloromethane, the Yevtushenko study (1976) and the epidemiologic study of Repko et al. (1976) indicate that chronic inhalation of chloromenthane by humans at the present TLV (100 ppm) may result in impaired neurologic functions. The EPA believes that an epidemiologic study would clarify the relationship between chronic exposure to chloromethane at 100 ppm and neurologic impairment. At this time, however, the EPA is not in a position to develop a test rule for such a study because of its current inability to identify suitable cohorts. NIOSH has attempted to locate a cohort for chloromethane and has thus far been unsuccessful (SRI 1979d). The EPA is proposing a rule under Section 8(a)(2)(F) of TSCA for chloromethane as well as other ITC chemicals. Under Section 8(a), the EPA may obtain readily accessible information from the files of manufacturers, processors and importers on the use, production and worker exposure from specified chemicals. The Agency will carefully evaluate the information received to determine if a cohort can be identified and if additional testing would then be considered necessary.

IV. Summary

A. Exposure

In 1979 approximately 497 million pounds of chloromethane were produced in the United States solely for domestic consumption. Hydrochlorination of methanol is the process used for greater than 98 percent of production. Chloromethane is used almost exclusively as an intermediate, primarily in the manufacture of silicones and tetramethyllead. Although chloromethane is present in the atmosphere in parts per trillion levels from natural sources, and in the parts per billion range from anthropogenic sources other than manufacturing, processing and use, high concentrations at the parts per million level have been found in occupational settings.

On the basis of chloromethane's almost exclusive use as an intermediate, reports prepared for NIOSH, and various reports of exposure found in the literature, the EPA staff concludes that the maximum potential for the possible risk associated with direct exposure to chloromethane exists during its manufacture, processing and use.

B. Health Effects

1. Systemic Effects

Chloromethane exposure has been reported to result in a wide range of systemic toxicity following both acute and chronic exposure. Although effects on the liver, kidney, heart and hematopoietic system have been demonstrated in both humans and animals, the most sensitive organ seems to be the CNS. The available animal studies appear to be adequate for determining chronic toxicity in systems other than the CNS.

2. Neurotoxicity

Chloromethane is a non-specific CNS depressant. There are human case reports, several animal studies, and controlled human laboratory studies that document its acute and chronic neurotoxicity. Chloromethane intoxication produces neurologic

signs, mood changes, and cognitive and intellectual deficits, as well as other symptoms. Chronic neurotoxicity, with a potential for permanent effects, is indicated by the evidence to be a risk to human health that cannot be assessed at this time without additional data, acquired by testing.

3. Mutagenicity

Chloromethane has been reported to possess mutagenic activity in bacterial systems that detect gene mutations and to cause chromosomal aberrations in higher plants. However, the evidence for chloromethane mutagenicity from this series of experiments is insufficient to permit a mutagenicity hazard assessment for chloromethane.

4. Oncogenicity

Neither epidemiology, other systemic human studies nor any animal assays have been reported which are sufficient to evaluate the oncogenic potential of chloromethane. However, there is substantial information suggesting that this chemical may possess oncogenic potential. This information includes evidence of its mutagenic activity, its *in vitro* and *in vivo* alkylating capabilities, and its structural relationship to known or suspected oncogens.

5. Teratogenicity

Because of the biologic activity of chloromethane in adults and its probable accessibility to the fetus, the EPA believes that chloromethane may present an unreasonable risk of teratogenicity. With regard to the teratogenic potential of chloromethane, the EPA is concerned with the danger of both structural malformations and behavioral alterations.

6. Metabolism

Although fragmentary research has been conducted in several areas of chloromethane metabolism, insufficient information exists to give a complete characterization. It is known that

chloromethane is absorbed through the airways and skin, that radioactivity can be detected to varying degrees in all tissues tested following inhalation of ^{14}C-chloromethane, and that excretion of unchanged compound is through the lungs, urine and feces, while possible metabolites also appear in the expired air and urine. A fraction of the inhaled radioactivity is retained by the organism following administration of $^{14}CH_3Cl$, and appears to be primarily bound to tissue sulfhydryl groups. Known metabolic products include methanol, formaldehyde, and formate. Although the EPA feels that metabolism studies on chloromethane are not complete, the Agency believes that the data available are sufficient at this time to assist in evaluating the risk of exposure to chloromethane.

7. Epidemiology

The EPA has determined that at ths time a suitable cohort for epidemiology studies cannot be identified and, therefore, is not requiring such studies. However, if information becomes available to the Agency through TSCA Section 8(a)(2)(F) leading to the identification of a suitable cohort, the Agency may reexamine this conclusion.

References Cited

Anonymous. 1945. Late effects of methyl chloride poisoning. J. Med. Assoc. 127:882.

Ahlstrom RC Jr, Steele JM. 1979. In: Standen A, ed. Kirk-Othmer encyclopedia of chemical technology, New York: Interscience Publishers, 3rd ed. Vol. 5, pp. 677-685.

Ahmed AE, Anders MW. 1978. Metabolism of dihalomethanes to formaldehyde and inorganic halide. II. Studies on the mechanism of the reaction. Biochem. Pharmacol. 27:2021-2025.

ACGIH. 1979. American Conference of Govermental Industrial Hygienists. Methyl chloride.

Andrews AW, Zawistowski ES, Valentine CR. 1976. A comparison of the mutagenic properties of vinyl chloride and methyl chloride. Mutat. Res. 40:273-276.

Arcos JC. 1978. Criteria for selecting chemical compounds for carcinogenicity testing: An essay. J. Environ. Pathol. Toxicol. 1:433-458.

Baker HM. 1927. Intoxication with commercial methyl chloride. J. Am. Med. Assoc. 88:1137-1138.

Barlow SM, Sullivan FM. 1975. Behavioral teratology. In: Berry CL, Poswillo DF, eds. Teratology: trends and applications. New York: Springer-Verlag, pp. 103-120.

Bartsch H. 1976. Predictive value of mutagenicity tests in chemical carcinogenesis. Mutat. Res. 38:177-190.

Battelle. 1979. Battelle Laboratories. A ninety-day inhalation toxicology study in F-344 albino rats and $B_6C_3F_1$ mice exposed to atomspheric methyl chloride gas. Research Triangle Park, NC: Chemical Industry Institute of Toxicology (CIIT).

Belova SF, Yevtushenko GY. 1967. Toxic effect of methyl chloride on the visual organ. Toksikol. Novykh Prom. Khim. Veshchestv 9:182-187. (In Russian; translation)

Birch CA. 1935. Methyl chloride poisoning. Lancet 228:259-260. Feb. 2, 1935.

Borghetti A, Gobbato F. 1969. Acute renal insufficiency from chlorinated derivatives of aliphatic hydrocarbons. Giornale Clin. Med. 50:463-487. (In Italian; translation)

Bornschein RL, Hastings L, Manson JM. 1980. Behavioral toxicity in the offspring of rats exposed to dichloromethane (DCM) prior to and/or during gestation. Toxicol. Appl. Pharmacol. 52:29-37.

Brewen JG, Payne HS, Jones KP, Preston RJ. 1975. Studies on chemically induced dominant lethality. I. The cytogenetic basis of MMS-induced dominant lethality in post-meiotic germ cells. Mutat. Res. 33:239-250.

Brusick D. 1979. Bacterial mutagenesis and its role in the identification of potential animal carcinogens. In: Griffin AC, Shaw CR, eds. Carcinogens: identification and mechanisms of action. New York: Raven Press, pp. 3-105.

Buelke-Sam J, Kimmel CA. 1979. Development and screening methods for behavioral teratology. Teratology 20:17-30.

Bus JS. 1979. Report to the methyl chloride steering committee: Disposition of ^{14}C-methyl chloride in rats and mice. Interim findings. Research Triangle Park, NC: Chemical Industry Institue of Toxicology (CIIT).

CIIT. 1977. Chemical Industry Institute of Toxicology A proposed toxicological evaluation of methyl chloride in laboratory animals. Research Triangle Park, NC: Chemical Industry Institute of Toxicology (CIIT).

CIIT. 1979. Chemical Industry Institute of Toxicology. TSCA Sec. 8(e) submission 8EHQ-1079-0314. Formalydehyde research findings. Washington DC: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

CMR. 1976. Chemical Marketing Reporter. Chemical profile- Methyl chloride. p. 9. March 29, 1976.

CMR. 1979. Chemical Marketing Reporter. Chemical profile - Methyl chloride. February 12, 1979.

Crandall MS. 1978. Walk-through industrial hygiene survey of monochlorobenzene and methyl chloride at Dow Chemical Company, Midland, Michigan. Cincinnati, OH: National Institute for Occupational Safety and Health.

CRC. 1978. CRC Handbook of Chemistry and Physics. 58th ed. Cleveland: CRC Press.

Cremieux L, Herman JA. 1974. Photolysis of gaseous ethyl chloride below and above the ionization potential. Can. J. Chem. 52:3098-3105. (In French).

Cronn DR, Rasmussen RA, Robinson E, Harsch DE. 1977. Halogenated compound identification and measurement in the troposphere and lower stratosphere. J. Geophys. Res. 82:5935-5944.

Chu EHY, Trosko JE, Chang CC. 1977. Mutational approaches to the study of carcinogenesis. J. Toxicol. Environ. Health 2:1317-1324.

Crandall. 1978. (see p. 73)

Davis LN, Strange JR, Hoecker JE, Howard PH, Santodonato J. Syracuse Research Corporation. 1977. Investigation of selected potential environmental contaminants: Monohalomethanes. Final report. SRC No. L1312-05. Washington, DC: U.S. Environmental Protection Agency. EPA 560/2-77-007.

DeForest EM. 1979. Chloromethanes. Encycl. Chem. Process. Des. Vol. 8. New York: Marcel Dekker, Inc. pp. 214-270.

Del Zotti G, Gillardi V. 1954. Hepatic function in workers of the refrigerating industry exposed to the inhalation of gases. Med. Lavoro 55: 350-356. (In Italian; translation)

Diamond Shamrock Chemical Company. 1978a. TSCA Sec. 8(d) submission 8DHQ-1078-0198. Chloromethane. In vitro and subacute in vivo host-mediated assay for mutagenesis. Bio/Tox. Washington DC: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

Diamond Shamrock Chemical Company. 1978b. TSCA Sec. 8(d) submission 8DHQ-1078-0196. Chloromethane. Dominant lethal study in rats. Bio/Tox. Washington DC: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

Dodd DE, Bus JS, Barrow CS. 1979. Alterations in tissue sulfhydryl concentrations in rats after acute inhalation exposure to methyl chloride. Pharmacologist 21:215.

Dow Chemical U.S.A. Product literature: material safety data sheet (June 23, 1978) and quality assurance sales specification (March 22, 1976) for methyl chloride. Midland, MI 48640

Drake JW. 1975. Environmental mutagenic hazards. Science 187: 503-514.

Druckrey H, Kruse H, Preussmann R, Ivankovic S, Landschutz C. 1970. Cancerogenic alkylating substances. III. Alkylhalide, -sulfate, -sulfonate and ring strained heterocyclic compounds. Z. Krebsforschung 74: 241-273. (In German; translation)

Dunn RC, Smith WW. 1947. Acute and chronic toxicity of methyl chloride IV. Histopathologic observations. Arch. Pathol. 43:296-300.

E.I. du Pont de Nemours and Company. 1977. TSCA Sec. 8(d) submission 8DHQ-1078-0204. Haskell Laboratory report on chloromethane mutagenicity test. Washington DC: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

Ethyl. (n.d.) Ethyl Corporation. Methyl chloride handbook. ICD-1051 (978). 451 Florida Blvd., Baton Rouge, LA 70801.

Fishbein L. 1977. Structural parameters associated with carcinogenesis (halogenated olefins, vinyl and allyl analogs and epoxides). In: Asher IM, Zervos C, eds. Structural correlates of carcinogenesis and mutagenesis. A guide to testing priorities? Proceedings of the second FDA Office of Science Summer Symposium. Washington DC: Food and Drug Administration, Department of Health, Education, and Welfare. pp. 8-21.

Flamm WG. 1977. Approaches to determining the mutagenic properties of chemicals: risk to future generations. J. Environ. Pathol. and Toxicol. 1:301-352.

Flury F. 1928. Modern industrial intoxications. Arch. Exp. Pathol. Pharmakol. 138:65-82. (In German; translation)

Gaultier M, Frejaville JP, LeBreton R, Garat J, Gervais P, Fournier E. 1965. On the difficulty of diagnosing certain mass poisonings. A case of familial poisoning from methyl chloride. Ann. Med. Leg. 45:273-275. (In French; translation)

Gerbis H. 1914. Peculiar conditions of narcosis following industrial use of methyl chloride. Muenchener Med. Wochensch. 61:879. (In German; translation)

Gralla EJ. 1979. Status of methyl chloride toxicology studies. CIIT Memorandum-number 15 to methyl chloride steering committee. Dec. 21, 1979. Research Triangle Park, NC: Chemical Industry Institute of Toxicology (CIIT).

Gudmundsson G. 1977. Methyl chloride poisoning 13 years later. Arch. Environ. Health 32:236-237.

Gummert M. 1961. The Wilson block after methyl chloride intoxication. Zeitschr. Ges. Inn. Med. Ihregrenzegebiete 16:677-680. (In German; translation)

Hansch C, Vittoria A, Silipo C, Jow P. 1975. Partition coefficients and the structure-activity relationship of the anesthetic gases. J. Medicinal Chem. 18:546-548.

Hansen H, Weaver NK, Venable FS. 1953. Methyl chloride intoxication. Arch. Ind. Hyg. Occup. Med. 8:328-334.

Hardin BD, Manson JM. 1980. Absence of dichloromethane teratogenicty with inhalation exposure in rats. Toxicol. Appl. Pharmacol. 52:22-28.

Harsch D. Washington State University. 1977. Study of halocarbon concentrations in indoor environments. Final report. Washington DC: Office of Research and Development. U.S. Environmental Protection Agency. Contract no. WA 6-99-2922-J.

Hartman TL, Wacker W, Roll RM. 1955. Methyl chloride intoxication. Report of two cases, one complicating pregnancy. N. Engl. J. Med. 253:552-554.

Hayhurst ER, Greenburg L. 1929. Poisoning from commercial methyl chloride. Am. J. Pub. Health 19:1048-1051.

Kegel AH, McNally WD, Pope AS. 1929. Methyl chloride poisoning from domestic refrigerators. J. Am. Med. Assoc. 93:353-358.

Klimkova-Deutschova E. 1957. Research of the neurological picture in methyl chloride poisoning. Rev. Czech. Med. 3:1-11.

Kubic VL, Anders MW. 1978. Metabolism of dihalomethanes to carbon monoxide. III. Studies on the mechanism of the reaction. Biochem. Pharmacol. 27:2349-2355.

Kucera J. 1968. Exposure to fat solvents: A possible cause of sacral agenesis in man. J. Pediat. 72:857-859.

Langauer-Lewowicka H, Manowska T, Dobrogowska-Kunicka J. 1974. Assessment of nervous system in persons exposed to the action of organic solvents. Neurol. Neurochir. Pol. 24: 559-564. (In Polish; translation)

Langman J, Webster W, Rodier P. 1975. Morphological and behavioral abnormalities caused by insults to the CNS in the perinatal period. In: Berry CL, Poswillo DE, eds. Teratology: trends and applications. New York: Springer-Verlag. pp. 182-200.

Laskowski S, Tomczewska-Wilk A, Ratajski W, Pohorski A. 1976. Methylchloride poisoning. Wlad. Lek. 29:59-62. (In Polish Translation)

Lawley PD. 1976. Carcinogenesis by alkylating agents. In: Searle CE, ed. Chemical carcinogens. ACS Monogr. 173, pp. 83-244.

Lovelock JE. 1975. Natural halocarbons in the air and in the sea. Nature 256:193-194.

Lowenheim FA, Moran MK. 1975. Faith, Keyes, and Clark's industrial chemicals, 4th ed. New York: Wiley Interscience, pp. 530-538.

MacDonald JDC. 1964. Methyl chloride intoxication. J. Occup. Med. 6:81-84.

Mackie IJ. 1961. Methyl chloride intoxication. Med. J. Australia I:203-205.

Malling HV, Chu EHY. 1974. Development of mutational model systems for study of carcinogenesis. In: Ts'o, PO, DiPaolo JA, eds. Chemical carcinogenesis. Part B. New York: Marcel Dekker, Inc. pp. 545-563.

McElheny VK, Abrahamson S, eds. 1979. Assessing chemical mutagens: the risk to humans. Banbury Report 1. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory.

McNally WD. 1946. Eight cases of methyl chloride poisoning with three deaths. J. Ind. Hyg. Toxicol. 28:94-97.

Merck Index. 1976. 9th ed. Rahway, NJ:Merck and Co., Inc.

Miller EC. 1978. Some current perspective on chemical carcinogenesis in humans and experimental animals: presidential address. Cancer Research 38:1479-1496.

Miller EC, Miller JA. 1974. Biochemical mechanisms of chemical carcinogenesis. In: Busch H. ed. The molecular biology of cancer. New York: Academic Press, Inc., pp. 377-402.

Miller JA. 1979. Concluding remarks on chemicals and chemical carcinogenesis. In: Griffin AC, Shaw CR, eds. Carcinogens: identification and mechanisms of action. New York: Raven Press, pp.455-469.

Mitchell RI, Pavkov KL, Kerno WD, Mitchell BR. Battelle. 1979. Interim report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride (6-month status). Research Triangle Park, NC: Chemical Industry Institute of Toxicology (CIIT).

Morgan A, Black A, Belcher DR. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann. Occup. Hyg. 13:219-233.

NAS. 1976. National Academy of Sciences. Halocarbons: effects on stratospheric ozone. Washington DC: National Academy of Sciences.

NAS. 1977. National Academy of Sciences Committee for the Revision of NAS Publication 1138. Principles and procedures for evaluating the toxicity of household substances. Washington, DC: National Academy of Sciences. pp. 86-98.

NAS. 1978. National Academy of Sciences. Nonfluorinated halomethanes in the environment. Washington DC: National Academy of Sciences.

NIOSH. 1977. National Institute for Occupational Safety and Health. Occupational diseases. A guide to their recognition. Washington DC: Department of Health, Education, and Welfare. (DHEW Publ. No. 77-181. NIOSH).

NIOSH. 1978. National Institute for Occupational Safety and Health. Computer printout: National Occupational Hazard Survey, 1972-1974. Retrieved Dec 5, 1978. Washington, DC: National Institute for Occupational Safety and Health.

Nishimura H, Tanimura T. 1976. Clinical aspects of the teratogenicity of drugs. Amsterdam: Excerpta Medica. p. 57.

Noro L, Pettersson T. 1960. Methyl chloride intoxication. Nordisk. Med. 14:381-384. (In Norwegian; translation)

NSF. 1975. National Science Foundation. Research program on hazard priority ranking of manufactured chemicals. Phase II - final report. Washington DC: National Science Foundation. NTIS No. PB 263 164.

OPTS. 1980. Office of Pesticides and Toxic Substances. Computer printout: CAS Number 74-87-3 Methane, chloro- : 1977 production data from the nonconfidential initial TSCA inventory. Retrieved via CICIS Feb. 29, 1980. Washington, DC: U.S. Environmental Protection Agency.

ORD. 1979. Office of Research and Development. Compilation of data from Athens ERL list of organic compounds identified in water. Retrieved Feb. 1979. Athens, GA: Environmental Research Laboratory, U.S. Environmental Protection Agency.

Palmer TY. 1976. Combustion sources of atmospheric chlorine. Nature 263:44-46.

Pegg AE. 1977. Formation and metabolism of alkylated nucleosides: possible role in carcinogenesis by nitroso compounds and alkylating agents. Advances in Cancer Res. 25:195-269.

Pohl LR, Bhooshan B, Whittaker NF, Krishna G. 1977. Phosgene: A metabolite of chloroform. Biochem. Biophys. Res. Commun. 79:684-691.

Pohl LR, George JW, Martin JL, Krishna G. 1979. Deuterium isotope effect in in vivo bioactivation of chloroform to phosgene. Biochem. Pharmacol. 28:561-563.

Pohl LR, Krishna G. 1978. Deuterium isotope effect in bioactivation and hepatotoxicity of chloroform. Life Sci. 23:1067-1072.

Poirier LA, Stoner GD, Shimkin MB. 1975. Bioassay of alkyl halides and nucleotide base analogs by pulmonary tumor response in strain A mice. Cancer Res. 35: 1411-1415.

Putz VR, Setzer JV, Croxton JS, Phipps FC. 1979. Methyl chloride/drug interactions on performance. I. Effects of acute low level methyl chloride exposure combined with diazepam on behavioral and neurological measures of human activation levels. Draft report. Washington, DC: National Institute for Occupational Safety and Health, U.S. Department of Health, Education, and Welfare.

Redford-Ellis M, Gowenlock AH. 1971a. Studies on the reaction of chloromethane with human blood. Acta Pharmacol. Toxicol. 30:36-48.

Redford-Ellis M, Gowenlock AH. 1971b. Studies on the reaction of chloromethane with preparations of liver, brain and kidney. Acta Pharmacol. Toxicol. 30:49-58.

Repko JD, Jones PD, Garcia LS, Schneider EJ, Roseman E, Corum CR. University of Louisville Performance Research Laboratory. 1976. Behavioral and neurologic effects of methyl chloride. Washington, DC: National Institute for Occupational Safety and Health, Department of Health, Education, and Welfare. DHEW (NIOSH) 77-125.

Reynolds ES, Yee AG. 1967. Liver parenchymal cell injury. V. Relationships between patterns of chloromethane-C^{14} incorporation into constituents of liver in vivo and cellular injury. Lab. Invest. 16:591-603.

Rosenkranz HS, Poirier LA. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J. Natl. Cancer Inst. 62:873-892.

Saita G. 1959. Prothrombin factors in acute poisoning by inhalation. Med. Lavoro 50:13-24. (In Italian; translation)

Scharnweber HC, Spears GN, Cowles SR. 1974. Chronic methyl chloride intoxication in six industrial workers. J. Occup. Med. 16:112-113.

Schwarz F. 1926. Instances of poisoning and animal experimentation with methyl chloride. Dtsche. Z. Ges. Gerichtl. Med. 7:278-288. (In German; translation)

Shamel RE, Williams R, O'Neill JK, et al. Arthur D. Little, Inc. 1975. Preliminary economic impact assessment of possible regulatory action to control atmospheric emissions of selected halocarbons. Research Triangle Park, NC: Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency. NTIS No. PB 247 115.

Sharp BB. 1930. Toxic effects of methyl chloride gas. Brit. Med. J., Feb. 22, 1930, p. 336.

Simmon VF. 1977. Structural correlations of carcinogenic and mutagenic alkyl halides. In: Asher IM, Zervos C, eds. Structural correlates of carcinogenesis and mutagenesis--A guide to testing priorities. Washington, DC: Department of Health, Education and Welfare. pp. 163-171.

Singer B. 1975. The chemical effects of nucleic acid alkylation and their relation to mutagenesis and carcinogenesis. Prog. Nucl. Acid Res. Molec. Biol. 15:219-284.

Singh HB, Salas LJ, Cabanagh LA. 1977. Distribution sources and sinks of atmospheric halogenated compounds. J. Air Pollut. Control Assoc. 27:332-336.

Singh HB, Salas LJ, Shigeishi J, Scribner E. 1979. Atmospheric halocarbons, hydrocarbons, and sulfur hexafluoride: Global distributions, sources and sinks. Science 203:899-903.

Sittig M. 1977. Pesticide process encyclopedia. Chemical technology review series. No. 81, pp. 76-78, 219-220, 335, 362.

Smith HH, Lotfy TA. 1954. Comparative effects of certain chemicals on Tradescantia chromosomes as observed at pollen tube mitosis. Amer J. Bot. 41:589-593.

Smith WW. 1947. The acute and chronic toxicity of methyl chloride. III. Hematology and biochemical studies. J. Ind. Hyg. Toxicol. 29:185-189.

Smith WW, von Oettingen WF. 1947a. The acute and chronic toxicity of methyl chloride. I. Mortality resulting from exposures to methyl chloride in concentrations of 4000 to 300 parts per million. J. Ind. Hyg. Toxicol. 29:47-52.

Smith WW, von Oettingen WF. 1947b. The acute and chronic toxicity of methyl chloride. II. Symptomatology of animals poisoned by methyl chloride. J. Ind. Hyg. Toxicol. 29:123-128.

Soucek B. 1961. Retention and excretion of methyl chloride and carbon tetrachloride in rats. Arch. Gewerbepath. Gewerbehyg. 18:370-383. (In German; translation)

Sperling F, Macri FJ, von Oettingen WF. 1950. Distribution and excretion of intravenously administered methyl chloride. Arch. Ind. Hyg. Occup. Med. 1:215-224.

Spevak L, Nadj V, Felle D. 1976. Methyl chloride poisoning in four members of a family. Brit. J. Ind. Med. 33:272-274.

Stanford Research Institute (SRI) (for NIOSH). Undated. Industrial hygiene assessment of selected chlorinated hydrocarbons project. Task 1 Report--methyl chloride.

SRI International (SRI) (for NIOSH). 1978a. Methyl chloride survey report of E.I. Dupont Corporation, Deepwater, New Jersey.

SRI International (SRI) (for NIOSH). 1978b. Methyl chloride survey report of Continental Oil Company, Conoco Chemicals, Westlake, Louisiana.

SRI International (SRI) (for NIOSH). 1978c. Methyl chloride survey report of General Electric Company, Waterford, New York.

SRI International (SRI) (for NIOSH). 1979a. Methyl chloride survey report of Conoco Chemicals, Westlake, Louisiana.

SRI International (SRI) (for NIOSH). 1979b. Methyl chloride survey report of the plant contact, Dow Corning Corporation, Midland, Michigan.

SRI International (SRI) (for EPA) (1979c). Atmospheric measurements of selected toxic organic chemicals. (Interim Report).

SRI International (SRI) (for NIOSH) (1979d). Methyl chloride survey report of the plant contact, E.I. Dupont Corporation, Deepwater, New Jersey.

Stewart RD, Hake CL, Wu A et al. The Medical College of Wisconsin. 1977. Methyl chloride: development of a biologic standard for the industrial worker by breath analysis. Washington, DC: National Institute for Occupational Safety and Health, Department of Health, Education, and Welfare. Contract no. HSM 99-72-84.

Sujbert L. 1967. Studies on the degradation of methyl chloride in mice. Arch. Toxikol. 22:233-235. (In German; translation)

Suntych F. 1956. Internal clinical picture of persons working with methyl chloride. Pracovni Lek. 8:91-95. (In Czechoslovakian; translation)

Suss R, Kinzel V, Scribner JD. 1973. Genetics and cancer. In Cancer: experiments and concepts. New York: Springer-Verlag, pp. 178-192.

Thordarson O, Gudmundsson G, Bjarnason O, Johannesson T. 1965. Methyl chloride poisoning. Nordisk Med. 73:150-154. (In Norwegian; translation)

Trontell A, Connery J. Energy Resources Co. Inc. 1979. Short-term tests for carcinogens, mutagens and other genotoxic agents. Research Triangle Park, NC: Health Effects Research Laboratory, U.S. Environmental Protection Agency. EPA 625/9-79-003.

Trosko JE, Chang CC. 1978. Relationship between mutagenesis and carcinogenesis. Photochem. Photobio. 28:157-168.

Trubecka G, Brzeski Z. 1968. Delirium syndrome in the course of methyl chloride intoxication. Med. Pracy 19:393-395. (In Polish; translation)

TSCA ITC. 1978. Toxic Substances Control Act Interagency Testing Committee. Initial report of the TSCA Interagency Testing Committee to the Administrator, EPA. Washington, DC: U.S. Environmental Protection Agency. NTIS No. PB 275 367.

USEPA. 1978a. U.S. Environmental Protection Agency. Office of Pesticides Programs. Ethylene oxide. Rebuttable presumption against registration; maximum residue limits and daily levels of exposure. Fed. Regist. Jan. 27, 1978, 43:3800.

USEPA 1978b. U.S. Environmental Protection Agency. Office of Pesticide Programs. Proposed guidelines for registering pesticides in the U.S. Hazard evaluation: humans and domestic animals. Fed. Regist., Aug. 22, 1978, 43:37336.

USEPA. 1979a. U.S. Environmental Protection Agency. Office of Toxic Substances. Proposed health effects test standards (acute and subchronic toxicity, mutagenic, teratogenic, and reproductive effects, and metabolism studies). Fed. Regist. July 26, 1979, 44:44054.

USEPA. 1979b. U.S. Environmental Protection Agency. Office of Toxic Substances. Proposed health effects test standards (chronic). Fed. Regist., May 9, 1979, 44:27334.

USEPA. 1979c. U.S. Environmental Protection Agency. Office of Water Planning and Standards. Halomethanes. Ambient water quality criteria. Draft proposal. Washington, DC: U.S. Environmental Protection Agency. (PB 296 797)

USITC. 1970-1975. U.S. International Trade Commission. Synthetic organic chemicals. United States production and sales. Washington, DC: U.S. Government Printing Office.

USOSHA. 1974. U.S. Occupational Safety and Health Administration. Occupational safety and health standards. 29 CFR 1910.1000, Table Z-2. p. 579 (1979 CFR).

van Raalte HGS, van Velzen HGECT. 1945. Methyl chloride intoxication. Ind. Med. 14:707-709.

van Stee EW. 1976. Toxicology of inhalation anesthetics and metabolites. Ann. Rev. Pharmacol. Toxicol. 16:67-79.

Villee C. 1971. Species differences in transport. In: Newburgh R, ed. Proceedings of a conference on toxicology: implications to teratology, Mar. 15-17, 1971, Gaithersburg, MD. Washington DC: National Institutes of Child Health and Human Development, Department of Health, Education, and Welfare. pp. 297-310.

von Oettingen WF. 1964. Halogenated hydrocarbons of industrial and toxicological importance. New York: Elsevier. pp. 5-25.

Vorhees CV, Brunner RL, Butcher RE. 1979a. Psychotropic drugs as behavioral teratogens. Science 205:1220-1225.

Vorhees CV, Brunner RL, Butcher RE, Sobotka TJ. 1979b. A developmental test battery for neurobehavioral toxicity in rats: a preliminary analysis using monosodium glutamate, calcium carrageenan and hydroxyurea. Toxicol. and Appl. Pharmacol. 50:267-282.

Walter B, Weiss A. 1951. Delayed results of acute methyl chloride intoxication. Med. Welt. 20:987-988. (In German; translation)

Weinstein A. 1937. Methyl chloride (refrigerator) gas poisoning J. Am. Med. Assoc. 108:1603-1605.

Weisburger J. 1977. A decision-point approach to carcinogen screening. In: Asher IM, Zervos C, eds. Structural correlates of carcinogenesis and mutagenesis. A guide to testing priorities? Washington, DC: Food and Drug Administration, Department of Health, Education, and Welfare (DHEW Pub. FDA 78-1046) pp. 45-54.

White JL, Somers PP. 1931. The toxicity of methyl chloride for laboratory animals. J. Ind. Hyg. Toxicol. 13:273-275.

Wiernikowski A, Korohoda J, Guzik E, Wojdyla Z. 1974. Collective intoxication with methyl chloride. Med. Pracy 25:571-573. (In Czechoslovakian; translation)

Wood MWW. 1951. Cirrhosis of the liver in a refrigeration engineer attributed to methyl chloride. Lancet, March 3, 1951: 508-509.

Yevtushenko GY. 1966. The toxicology of methyl chloride. Gig. Tr. Prof. Zabol. 10:20-25. (In Russian; translation)

Yevtushenko GY. 1967. Metabolism of methyl chloride. Farmakol. Toksikol. 30:239-240. (In Russian; translation)

References Reviewed But Not Cited in Support Document

Allied Chemical. 1978. Chloromethane. TSCA Sec. 8(d) submission 8DHQ-0978-0183. Washington, DC: Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

Anders MW, Kubic VL, Ahmed AE. 1977. Metabolism of halogenated methanes and macromolecular binding. J. Environ. Pathol. Toxicol. 1:117-124.

Anonymous. 1932. Refrigerants tested for toxicity. Ind. Eng. Chem. News Ed. 10:3-4.

Baker HM. 1930. Industrial methyl chloride poisoning. Amer. J. Public Hlth. 20:291-295.

Bakhishev GN. 1973. Relative toxicity of certain halogen derivatives of aliphatic hydrocarbons for rats. Farmakol. Toksikol. 8:140-142. (Russian)

Bakhishev GN. 1975. The correlation between the chemical structure and toxicity of some halogenated aliphatic hydrocarbons. Fiziol. Akt. Veshchestva 7:35-36. (Russian)

Balasubramanian D, Wetlaufer DB. 1966. Reversible alteration of the structure of globular proteins by anaesthetic agents. Proc. Natl. Acad. Sci. 55:762-765.

Battigelli MC, Perini A. 1955. Two cases of acute methyl chloride poisoning. Med. Lavoro 46:646-652. (Italian)

Berthelsen HC, Hansen OE, Lindeberg B. 1964. Methyl chloride intoxication. Ugeskr. Laeg. 126:134-138. (Danish)

Borovska D, Jindrichova J, Klima M. 1976. Methyl chloride intoxications in the East Bohemia district. Z. Gesamte Hyg. 22:241-245. (Czechoslovakian)

Chalmers JNM, Gillam AE, Kench JE. 1940. Porphyrinuria in a case of industrial methyl chloride poisoning. Lancet II:806-807.

Chalupa B, Synkova J, Sevcik M. 1960. The assessment of electroencephalographic changes and memory disturbances in acute intoxications with industrial poisons. Brit. J. Indust. Med. 17:238-241.

Cicerone RJ, Stedman DH, Stolarski RS. 1975. Estimate of late 1974 stratospheric concentration of gaseous chlorine compounds (ClX). Geophys. Res. Lett. 2:219-222.

Cronn DR, Harsch DE. 1976. Rapid determination of methyl chloride in ambient air samples by GC-MS. Anal. Lett. 9:1015-1023.

Crutzen PJ, Isaksen ISA, McAfee JR. 1978. The impact of the chlorocarbon industry on the ozone layer. J. Geophys. Res. 83:345-363.

Deinzer M, Schaumberg F, Klein E. 1978. Environmental health sciences center task force review on halogenated organics in drinking water. Environ. Hlth. Perspect. 24:209-239.

Dilling WL. 1977. Interphase transfer processes. II. Evaporation rates of chloro methanes, ethanes, ethylenes, propanes and propylenes from dilute aqueous solutions. Comparisons with theoretical predictions. Environ. Sci. Technol. 11:405-409.

Derwent RG, Eggleton AEJ. 1978. Halocarbon lifetimes and concentration distributions calculated using a two-dimensional tropospheric model. Atmospher. Environ. 12:1261-1269.

Dmitriev VI, Korshunov NN, Negoda PF, Kuzmenko NA, Petrenko DS. 1978. Thermal detoxication of waste gases from production of lower chloromethanes. Khimicheskaya teknuol. 4:57-58. (Russian)

Florescu A. 1967. Methyl chloride poisoning. Neurol. Psihiat. Neurochir. 12:431-434. (Romanian)

Fokina KV. 1967. The functional state of the olfactory and vestibular analyzers on exposure to the chlorine derivative of methane. Gig. I Sanit. 32:22-26. (Russian)

Goldbach HJ. 1949. Methylchloride poisoning. Med. Klin. 44:274-277. (German)

Gorham AP. 1934. Medical aspects of methyl chloride. Brit. Med. J. I:529-530.

Hanke J. 1967. Activities of serum enzymes in patients poisoned with various organic compounds. Med. Pracy 18:224-232. (Polish)

Henschler D. 1977. Toxicology of chlorinated solvents. In: Fukushima Y, ed. Science for better environment. Proceedings of the international congress on the human environment (HESC). Kyoto, Japan, Nov. 17-26, 1975. New York: Pergamon Press, pp. 490-504.

Hermann H, Vial J. 1935. New cases of cardiac syncope induced by the toxic association of epinephrine and different volatile organic compounds. Compt. Rend. Soc. Biol. 119:1316-1317. (French)

Hunter MJ. 1973. Perspectives of organosilicon chemistry: an industrial point-of-view. Intra-Science Chem. Rept. 7:45-54.

Irish DD. 1963. Methyl chloride. In: Patty FA, ed. Industrial hygiene and toxicology. Vol. 2, 2nd ed. New York: Interscience. pp. 1248-1251.

Ivanova-Tikhvinskaya YL. 1968. Change in pigment and protein metabolism upon toxic liver damage by a combination of substances used in the synthetic rubber industry. Gig. Tr. Prof. Zabol. 12:31-35. (Russian)

Johnson WR, Hale RW, Nedlock JW, Grubbs HJ, Powell DH. 1973. The distribution of products between mainstream and sidestream smoke. Tobacco Sci. 17:141-144.

Kolkmann FW, Volk B. 1975. Necroses in the granular cell layer of the cerebellum due to methylchloride intoxication in guinea pigs. Exp. Pathol. 10:298-308. (German)

Manufacturing Chemists Association (MCA). 1970. Methyl chloride. Chemical safety data sheet SD-40. Washington, DC: Manufacturing Chemists Association.

Marks E, Pawlak Z. 1964. Methyl chloride intoxication in the light of our own case. Med. Pracy 15:339-342. (Polish)

Mendeloff J. 1952. Death after repeated exposures to refrigerant gases. AMA Arch. Ind. Hyg. Occup. Med. 6:518-524.

Montemartini G. 1940. Experimental methyl chloride (CH_3Cl) poisoning. Note I. Introduction and histological findings. Ann. Med. Nav. 46:336-342. (Italian)

Morgan A, Black A, Belcher DR. 1972. Absorption of halogenated hydrocarbons and their excretion in breath using chlorine -38 tracer techniques. Ann. Occup. Hyg. 15:273-283.

Murray AJ, Riley JP. 1973. Occurrence of some chlorinated aliphatic hydrocarbons in the environment. Nature 242:37-38.

Muscat-Baron JM. 1963. A case of methyl chloride poisoning. Brit. Med. J. III:365-366.

National Institute of Occupational Safety and Health (NIOSH). 1978. Letter on methyl chloride survey reports.

Nedvizhenko AA. 1968. The problem of acute methyl chloride poisoning. Gig. Tr. Prof. Zabol. 12:51-52. (Russian)

Newsome JR, Norman V, Keith CH. 1965. Vapor phase analysis of tobacco smoke. Tobacco Sci. 9:102-110.

Nozdrachev SI. 1974. Activity of glycolytic enzymes in methyl chloride poisoning. Farmakol. Toksikol. 37:98-100. (Russian)

Philippe RJ, Hobbs ME. 1956. Some components of the gas phase of cigarette smoke. Anal. Chem. 28:2002-2006.

Pohl LR, Krishna G. 1978. Study of the mechanism of metabolic activation of chloramphenicol by rat liver microsomes. Biochem. Pharmacol. 27:335-341.

Pohl LR, Nelson SD, Krishna G. 1978. Investigation of the mechanism of the metabolic activation of chloramphenicol by rat liver mirosomes. Identification of a new metabolite. Biochem. Pharmacol. 27:491-496.

Porteous HB. 1930. Toxic effects of methyl chloride gas. Brit. Med. J. I:414-415.

Rasmussen RA, Harsch DE, Sweany PH, Krasnec JP, Cronn DR. 1977. Determination of atmospheric halocarbons by a temperature-programmed gas chromatographic freezeout concentration method. J. Air Pollut. Control Assoc. 27:579-581.

Repko JD, Lasley SM. 1979. Behavioral, neurological and toxic effects of methyl chloride: a review of the literature. CRC Critical Rev. in Toxicol. 6:283-302.

Roche L, Bouchet J. 1948. Methyl chloride poisoning. Arch. Mal. Prof. Med. Travail Sec. Soc. 9:406-413. (French)

Rodman JF, Andrews KE. 1969. British patent specification No. 1 300 929. Production of foamed thermoplastics. London: Patent Office.

Rohrschneider L, Jaeschke A, Kubik W. 1971. Examination of air pollution at levels of up to 500 meters above industrial areas. Chem. Ing. Tech. 43:1010-1017. (German)

Roth B, Klimkova-Deutschova E. 1964. The effect of chronic exposure to industrial poisons on the electroencephalogram in man. Cesk. Neurol. 27:40-47. (Czechoslovakian)

Severs LW, Skory LK. 1975. Monitoring personnel exposure to vinyl chloride, vinylidene chloride and methyl chloride in an industrial work environment. Amer. Indust. Hyg. Ass. J. 36:669-676.

Shold DM, Rebbert RE. 1978. The photochemistry of methyl chloride. J. Photochem. 9:499-517.

Simmon VF, Kauhanen K, Tardiff RG. 1977. Mutagenic activity of chemicals identified in drinking water. In: Scott D, Bridges BA, Sobels FH, eds. Progress in genetic toxicology. New York: Elsevier/North-Holland. pp. 249-258.

Simmon VF, Tardiff RG. 1978. The mutagenic activity of halogenated compounds found in chlorinated drinking water. Water Chlorination. 2:417-431.

Spence JW, Hanst PL, Gay BW Jr. 1976. Atmospheric oxidation of methyl chloride, methylene chloride and chloroform. J. Air Pollut. Control Assoc. 26:994-996.

SRI International (SRI) (for NIOSH). 1978. Methyl chloride survey report of the plant contact. Dow Corning Corporation. Midland, Michigan.

Szoslandowa W. 1972. A case of methyl chloride intoxication. Klin. Oczna 42:1051-1053. (Polish)

Thomas E. 1960. Changes in the nervous system in the presence of intoxication due to low halide hydrocarbons. Anatomic studies of methyl chloride intoxication. Dtsche. Z. Nerv. 180:530-561. (German)

USEPA. 1978. Environmental Protection Agency. Report on environmental investigation of Boyer home, Pevely, Missouri.

USEPA. 1979. Environmental Protection Agency. CHIP document: Formaldehyde. Washington, DC: Office of Toxic Substances, U.S. Environmental Protection Agency.

von Oettingen WF, Powell CC, Sharpless NE, Alford WC, Pecora LJ. 1949. Relation between the toxic action of chlorinated methanes and their chemical and physicochemical properties. Natl. Inst. Hlth. Bull. 191:1-82.

von Oettingen WF, Powell CC, Sharpless NE, Alford WC, Pecora LJ. 1950. Comparative studies of the toxicity and pharmacodynamic actions of chlorinated methanes with special reference to their physical and chemical characteristics. Arch. Int. Pharmacodyn. 81:17-34.

Zahradnik M. 1965. Intoxication psychosis after methyl chloride. Cesk. Psychiat. 61:408-411. (Czechoslovakian)

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1 REPORT NO	2	3. RECIPIENT'S ACCESSION NO.
EPA-560/11-80-015		

4 TITLE AND SUBTITLE	5. REPORT DATE
Support Document Health Effects Test Rule: Chloromethane	June 1980 (approved)
	6. PERFORMING ORGANIZATION CODE
7 AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO
9 PERFORMING ORGANIZATION NAME AND ADDRESS Assessment Division Office of Pesticides and Toxic Substances 401 M Street, SW Washington, DC 20460	10. PROGRAM ELEMENT NO.
	11 CONTRACT GRANT NO
12 SPONSORING AGENCY NAME AND ADDRESS U. S. Environmental Protection Agency 401 M Street, SW Washington, DC 20460	13. TYPE OF REPORT AND PERIOD COVERED
	14 SPONSORING AGENCY CODE

15 SUPPLEMENTARY NOTES

16 ABSTRACT

In 1979 approximately 497 million pounds of chloromethane were produced in the United States solely for domestic consumption. It is used almost exclusively as an intermediate, primarily in the manufacture of silicone and tetramethyllead.

Chloromethane exposure has been reported to result in a wide range of systemic toxicity following both acute and chronic exposure. Although effects on the liver, kidney, heart, and hematopoietic system have been demonstrated in both humans and animals, the most sensitive organ seems to be the central nervous system (CNS).

Chloromethane has been reported to possess mutagenic activity in bacterial systems that detect gene mutations and to cause chromosomal aberration.

Evidence of its mutagenic activity, its in vitro and in vivo alkylating capabilities, and its sturctural relationship to known or suspected oncogens suggest that chloromethane may possess oncogenic potential.

EPA is also concerned with the danger of both structural malformation and behavioral alterations that may be posed by chloromethane.

Bibliography included.

17 KEY WORDS AND DOCUMENT ANALYSIS

a DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18 DISTRIBUTION STATEMENT	19 SECURITY CLASS (This Report)	21 NO. OF PAGES
Release unlimited.	unclassified	
	20 SECURITY CLASS (This page)	22. PRICE
	unclassified	

EPA Form 2220-1 (9-73)

*U S GOVERNMENT PRINTING OFFICE: 311-726/3904